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# **Tooth Loss Strongly Associates With Malnutrition in Chronic Kidney Disease**

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# **Abstract**

**Background—**In chronic kidney disease (CKD), inadequate nutritional intake, inflammation, and increased oxidative stress have been the major contributing factors in malnutrition pathogenesis. However, there is still a paucity of evidence assessing the magnitude of the effect of tooth loss on malnutrition in CKD populations. The authors hypothesize that among patients with CKD, tooth loss may affect nutritional status, using the National Health and Nutrition Examination Survey 1988 to 1994 (NHANES III).

**Methods—**Glomerular filtration rate (GFR) was estimated based on cystatin C levels using the relevant equation. Urinary albumin-to-creatinine ratio (albuminuria) was calculated in milligrams per gram with a cutoff point of 30 mg/g. CKD was defined based on estimated GFR <60 mL/ minute/1.73m<sup>2</sup> and albuminuria 30 mg/g. The cutoff point for serum albumin was set at 3.7 g/dL. Tooth loss categories were based on the number of missing and replaced teeth.

**Results—**A total of 2,749 patients was included and stratified based on their oral health status. There was a statistically significant correlation between tooth loss and the proportion of patients with low protein and caloric intake  $(P = 0.02$  and 0.01, respectively). Serum albumin reached a frequency peak in the fully edentulous group without dentures (group 4, 19.2%). In the same group, individuals had lower protein (30.1%) and caloric intake (30.2%) ( $P = 0.01$  and 0.02, respectively). Furthermore, logistic regression analysis confirmed the significant role of tooth loss on serum albumin and protein and energy intake in this population even after adjusting for confounding variables.

**Conclusion—**Tooth loss independently predicts low energy and protein intake, as well as serum albumin levels, biomarkers of malnutrition in CKD.

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# **Keywords**

Malnutrition; nutrition surveys; renal insufficiency; chronic; tooth loss

Chronic kidney disease (CKD) is characterized by protein–energy malnutrition and chronic inflammation, as well as high rates of cardiovascular mortality described as the malnutritioninflammation-atherosclerosis syndrome.<sup>1</sup> The prevalence of this syndrome in CKD ranges from 18% to 75%.<sup>2</sup> Several mechanisms, including inadequate nutritional intake, inflammation, increased oxidative stress, and increased catabolic response, have been established as the major contributing factors in malnutrition pathogenesis in  $CKD$ .<sup>3–5</sup> Uremia and uremic toxins inhibit the intake of carbohydrates, proteins, and nutritional solutions, causing anorexia, the loss of desire to eat.<sup>6</sup> Additionally, inflammatory cytokines act directly on peripheral sites as well as the hypothalamus by inhibiting appetite.<sup>6</sup> Inflammatory cytokines have been shown to trigger apoptosis and downregulate production of albumin mRNA by the liver, leading to reduced synthesis and increased albumin catabolism and vascular permeability.<sup>7,8</sup> Metabolic acidosis commonly associated with CKD is another mechanism that irreversibly stimulates protein degradation, also leading to low albumin levels.<sup>9</sup> Moreover, psychologic factors such as depression have been implicated in inadequate caloric intake in CKD.10 As a result, malnutrition is an important focus in CKD management as confirmed by the guidelines established by the National Kidney Foundation.<sup>11</sup>

Although uremia is known to affect appetite regulation<sup>12</sup> and taste (uremic hypogeusia),<sup>13</sup> there is a paucity of evidence in the nephrology literature assessing the magnitude of tooth loss on malnutrition in the CKD population.

Poor oral health leading to tooth loss directly affects chewing capacity and mastication forces, resulting in reduced nutritional intake and poor nutritional status.14–18 The authors hypothesize that among patients with CKD, tooth loss and poor oral health may affect nutritional status. This hypothesis was examined in a large, representative CKD sample of the United States population using the National Health and Nutrition Examination Survey 1988 to 1994 (NHANES III).<sup>19</sup>

# **MATERIALS AND METHODS**

#### **Study Population**

NHANES, a periodic survey conducted by the Centers for Disease Control and Prevention (CDC), provides cross-sectional national estimates of health and nutritional status of the civilian, non-institutionalized population.19 Individuals participate in interviews conducted at home and in extensive physical examinations, including blood and urine collection, performed at an examination center. NHANES III was conducted in two phases: 1988 to 1991 and 1991 to 1994. The protocols of NHANES were approved by the National Center for Health Statistics institutional review board, and written informed consent was obtained from all participants.<sup>19</sup> This study includes patients: 1) with CKD; 2) > 30 years; and 3) with no missing relevant variables such as oral examination, medical, and laboratory data.

Information on age, sex, race, and smoking history was based on self-report during the survey interview. A binary age variable was constructed using a cutoff point of 60 years based on risk assessment for CKD.20 Smoking status was determined using the answers to the questions: "Have you smoked at least 100 cigarettes in your life?" and "Do you smoke cigarettes?" Individuals who answered "no" to both questions were considered neversmokers. Individuals who answered "yes" to both questions were considered current smokers, whereas the ones, who only answered "yes" to the first question, were considered past-smokers. Additionally, diabetes was defined based on the answer to the question: "Have you been told by your doctor that you have diabetes?" Glycated hemoglobin was used as an indicator of diabetes control, with a cutoff of  $6.5\%$ .<sup>21</sup> A variable for diabetes duration was constructed using a previously used cut point of 10 years.<sup>22</sup> Education and income variables were constructed as reported previously,  $2<sup>3</sup>$  whereas body mass index (BMI) was calculated as body weight (kg) divided by squared height  $(m^2)$  and was stratified into five standard categories: low (<18.5), normal (18.5 to 24.9), overweight (25.0 to 29.9), obese (30.0 to 34.9), and morbidly obese ( $\,35.0$ ).<sup>24</sup>

# **Tooth Loss Definition**

Tooth loss has been considered a tangible, true endpoint<sup>25</sup> and indicator of poor oral health. The fully dentate status represents 28 natural teeth rather than 32 teeth, since third molars were not included in NHANES III dental examination protocols.

The five categories used for tooth loss and replacement stratification were: group  $0 =$ complete natural dentition; group  $1 =$  complete mixed dentition (natural teeth and replaced teeth); group  $2 =$  incomplete (natural or mixed) dentition; group  $3 =$  fully edentulous with full dentures; and group  $4 =$  fully edentulous with no dentures.<sup>26</sup> Further, in the regression analyses, tooth loss was represented by number of missing teeth used as a continuous variable.

# **Denture Type**

Full or partial denture was defined based on the denture type variables of the NHANES examination file for maxillary and mandibular teeth.

## **Diet**

Dietary data were extracted from the NHANES III diet surveys including the food frequency questionnaire and the 24-hour dietary recall. Variables were constructed representing the protein and energy intake with a cutoff point of 1.2 g/kg/day and 30 kcal/kg/day, respectively, as determined by CKD guidelines. <sup>11</sup>

### **Kidney Function**

Estimated glomerular filtration rate (eGFR) based on cystatin C levels has been shown to be independent of age and race, contrary to estimated GFR based on serum creatinine levels.<sup>27</sup> Thus, GFR was estimated based on cystatin C levels using the equation  $76.7 \times$  cystatin C−1.19.27 eGFR is reported in mL/minute/1.73m<sup>2</sup> . Urinary albumin-to-creatinine ratio (albuminuria) was calculated in milligrams per gram with a cutoff point of 30 mg/g.<sup>28</sup> All eGFR values > 200 mL/minute/1.73m<sup>2</sup> were truncated at that level.<sup>28</sup>

# **CKD Definition**

CKD was defined based on the recent classification that combined eGFR values  $<$ 60 mL/ minute/1.73m<sup>2</sup> and albuminuria 30 mg/g.<sup>20</sup> Cutoff points for CKD stages followed the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.20 More specifically, the CKD cutoff points are described as: Stage 1 (eGFR > 90 mL/minute/1.73m<sup>2</sup> and albuminuria); Stage 2 (eGFR 60 to 89 mL/minute/1.73m<sup>2</sup> and albuminuria); Stage 3A1 (eGFR 30 to 59 mL/minute/1.73m<sup>2</sup> and no albuminuria); Stage 3A2 (eGFR 30 to 59 mL/ minute/1.73m<sup>2</sup> and albuminuria); Stage 4A1 (eGFR < 30 mL/minute/1.73m<sup>2</sup> and no albuminuria); and Stage  $4A2$  (eGFR <30 mL/minute/1.73m<sup>2</sup> and albuminuria).<sup>20</sup>

# **Serum Albumin Levels**

Because serum albumin has been reported as a reliable systemic marker of malnutrition,29 a dichotomous variable was constructed representing serum albumin levels with a cutoff point of 3.7 g/dL based on the current definition for malnutrition in CKD.<sup>11</sup>

#### **Statistical Analyses**

Analyses were performed using statistical software<sup>||</sup> with a complex sample module incorporating sampling weights in the NHANES dataset.<sup>30</sup> Categorical variables were tested with the Pearson  $\chi^2$  test, and continuous variables were tested with the *t*-test for independent samples. Three logistic regression analyses were applied in the population: crude model (unadjusted); model 1: adjusted for age, sex, and race; and model 2 (full model) based on previous evidence<sup>28,31,32</sup> fully adjusted for age, sex, race, diabetes status, BMI, smoking, CKD status, denture status, education, and income. A non-automated stepwise regression model was used to assess the association of tooth loss (used as a continuous variable) with serum albumin as well as protein and energy intake. Sequence relevant confounders were added to produce the full model. For the categorical confounding variables, odds ratios (ORs) and 95% confidence intervals (CIs) were presented. For tooth loss, OR and 95% CI were calculated for every five teeth lost. More specifically, aged <60 years, female sex, non-Hispanic white race, absence of diabetes, normal BMI, CKD Stage 1A1, never-smoker status, natural dentition, high income, and education >12 years were used as referents in the regression models. Given the effect of decreased kidney function on malnutrition,<sup>33</sup> an exploratory analysis was performed on the effect modification of CKD status and tooth loss on the dependent variables.  $P$  values of <0.05 were accepted as statistically significant in all analyses.

# **RESULTS**

#### **Descriptive Analyses**

Of the total NHANES III study population (39,695), 2,749 patients fulfilled the inclusion criteria. Descriptive characteristics of the study sample stratified by tooth loss status are presented in Table 1. An overall descriptive analysis showed that the more missing teeth, the higher the proportion of patients with low protein and caloric intake. Albumin, a biomarker

<sup>||</sup>Predictive Analytics Software (PASW), v.18, IBM, Chicago, IL.

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of malnutrition, reached a frequency peak (19.2%) in group 4, characterized by fully edentulous individuals without dentures. Also, when comparing number of missing teeth in groups 1 and 2, individuals in group 2 were found to have statistically significant more missing teeth than individuals in category 1 ( $P = 0.001$ ).

When observing the fully dentate group 0 (405 patients), which represents the group with the best oral health status, most of the individuals were never-smokers with normal BMI, low diabetes prevalence, and medium income as well as dental visits that were not erratic. The demographics of this group predominantly revealed mainly non-Hispanic white patients aged  $<60$  years.

In group 1 (867 patients), which was characterized by mixed dentition with mean tooth loss of 2.1 teeth, the patients were predominantly non-Hispanic white, aged  $\leq 60$  years, with normal BMI and low diabetes prevalence. Furthermore, this group had a low frequency of reduced protein and caloric intake.

Group 2 (886 patients) was characterized by incomplete natural dentition and no replaced teeth, with mean tooth loss of 5.9 teeth. In this group, the demographics revealed higher frequency of patients aged >60 years (25.2%), predominantly non-Hispanic white. This group was characterized by a higher frequency of low protein and caloric intake compared with groups 0 and 1.

The behavioral and socioeconomic descriptive analyses revealed that groups 0 to 2 were characterized by medium income, and in a majority, good perception of health and >12 years of education. These findings positively correlated with oral health status as shown in Table 1.

Group 3 (543 patients who were fully edentulous with full dentures) was aged >60 years (78.9%) and mainly a non-Hispanic white population. In this group, 64.4% had low income and 56.0% had <12 years of education. More importantly, this group was characterized by the high proportion of patients with serum albumin <3.7 g/dL (17.5%). The vast majority of this group included overweight or obese patients as assessed by BMI, as well as patients with erratic dental visits (95.2%).

Group 4 (48 patients who were fully edentulous without full dentures) showed a high prevalence of individuals older than 60 years old. Of the patients with diabetes, 80.4% had the disease >10 years. Almost 50% of the individuals in this group were current smokers. Most of the patients in the group belonged to the low-income category (95.5%), with education <12 years (67%) and erratic dental visits (96.7%).

#### **Multivariate Models**

In the multivariate logistic regression model with serum albumin as a dependent variable (Table 2), missing teeth emerged as a significant predictor  $(P = 0.0001)$ , which sustained significance in the full model 2 ( $P = 0.001$ ) adjusting for denture status as well as all relevant confounders. When examining the confounding factors, model 1 confirmed the significant role of age (OR = 1.91, 95% CI 1.26 to 2.91), sex (OR = 2.62, 95% CI 1.82 to

3.78), and race  $(OR = 2.91, 95\% \text{ CI } 2.07 \text{ to } 4.08)$  in this association. In model 2, age and race sustained significance and BMI appeared as a significant predictor as expected. When the biologic effect of CKD status on serum albumin was tested in interaction with tooth loss, the interaction showed a trend to significance  $(P = 0.10)$ . In a subgroup analysis, tooth loss was a significant predictor in CKD Stage  $3A2 (P = 0.007)$  (data not shown).

In the logistic regression model in which caloric intake was used as a dependent variable (Table 3), tooth loss emerged as a significant predictor  $(P = 0.0001)$  and sustained statistical significance in all models ( $P = 0.03$  and  $P = 0.01$  in models 1 and 2, respectively) after adjusting for denture status. When examining the confounding factors, sex appeared significant in model 1 and lost significance in model 2, whereas diabetes and BMI were significant predictors in model 2 (Table 3). When the biologic effect of CKD as a modifier of the model was tested in interaction terms with tooth loss, the interaction did not appear significant  $(P = 0.29)$  (data not shown).

Furthermore, in the logistic regression model in which protein intake was the dependent variable, number of missing teeth emerged as a statistically significant predictor in the crude analysis ( $P = 0.03$ ), model 1 ( $P = 0.01$ ), and the full model 2 ( $P = 0.02$ ) (Table 4). When assessing the confounding factors, sex was a significant predictor in model 1 and sustained significance in model 2 together with BMI (Table 4). When interaction between CKD status and tooth loss was tested, the results did not reach significance (data not shown).

Further, ORs and 95% CIs were calculated for every five teeth lost, and in all models the variable maintained significance (Tables 2 through 4). Overall, the regression models confirmed the impact of tooth loss on the dietary intake in this population.

# **DISCUSSION**

This is the first study of a nationally representative CKD sample of the United States population to show that poor oral health status independently predicted malnutrition in patients with CKD after controlling for confounding factors. For the first time in CKD populations, the current authors showed that the more teeth lost, the worse the dietary intake. In the mixed dentition group (group 1), in which missing teeth were replaced by partial dentures or fixed crowns, the dietary intake was similar to the reference group of good oral health, confirming the importance of chewing function. The fully edentulous group without full dentures (group 4) showed the highest proportion of patients with low protein and caloric intake due to the compromised chewing capacity. These results are also consistent with previous studies in the general population where individuals with fewer teeth tend to have compromised nutrient intake as well as compromised general nutritional status.<sup>34</sup> Furthermore, dental status has been shown to affect eating ability<sup>35</sup> as shown by reduced protein and energy.

Malnutrition in CKD is a complex phenomenon that may be mediated by several biologic mechanisms, including uremic toxicity, systemic inflammation, and central anorexia.<sup>36</sup> Others factors such as depression, use of appetite-suppressing medications, and behavioral factors influencing the desire to eat have been reported as contributing to anorexia in

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CKD.12 The present study is the first population-based study examining the effect of chewing ability on nutritional intake and bio-markers of malnutrition in CKD. Thus, these data extend the understanding of the factors that contribute adversely to nutritional status in individuals with CKD.

Although serum albumin had been widely accepted as a marker of malnutrition in the past, more recently hypoalbuminemia is also recognized to be a manifestation of systemic inflammation. For example, even in extreme conditions such as starvation or marasmus, serum albumin levels remain normal. The direct relationship of albumin with malnutrition becomes manifest only in extremely deficient dietary-complicated conditions that also have an inflammatory component, such as kwashiorkor.<sup>7,37</sup> Inflammatory disorders have a contributing role in the liver by decreasing albumin synthesis affected by acute-phase proteins as well as interleukin- $1^{38}$  and by increasing albumin catabolism.<sup>33</sup> The current results confirm the effect of poor oral health, evident by tooth loss, on hypoalbuminemia even after controlling for other confounders.

In this study, group 4 overwhelmingly represents elderly individuals with longstanding and poorly controlled diabetes, high proportion of current smokers, erratic dental visits, and more advanced CKD stages. In this extreme group, one could extrapolate the results and anticipate a natural history of tooth loss when the patients progress to dialysis stage.

Based on this study, the authors propose two potential mechanisms that could link oral health status to malnutrition and inflammation in CKD: 1) a direct pathway in which tooth loss could directly affect nutritional intake; and 2) an indirect pathway through which the systemic inflammatory response caused by oral infections such as periodontitis could elicit a combination of positive and negative acute-phase proteins by the liver, promoting protein catabolism and contributing to malnutrition.

A limitation of this study is the cross-sectional design that prevented the assessment of temporal or causal relationships. Moreover, the NHANES data prevent us from assessing direct chewing capacity as measured by occluding tooth pairs. To overcome this limitation, the authors focused on evaluating the impact of tooth loss on nutritional intake after adjusting for partial or full dentures. Additionally, this study includes only predialysis CKD populations because of NHANES III database limitations. Given that malnutritioninflammation-atherosclerosis has been a highly important disorder in hemodialysis, one would expect more pronounced oral health–malnutrition associations in hemodialysis populations. Hence, further research addressing the oral health role on malnutrition– inflammation would be necessary in patients undergoing hemodialysis. At the predialysis stage, the effect of oral health status on progression of CKD and prevention of malnutrition would be an essential field of interest. Long-term prospective studies as well as interventional studies are needed to fully assess the possible causal relationships among oral health status, malnutrition, and systemic inflammation in the CKD population.

# **CONCLUSIONS**

This study specifically highlights the critical role of oral health on malnutrition in CKD. Furthermore, it shows that poor oral health as manifested by tooth loss predicts reduced nutritional and caloric intake in CKD.

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Clinicopathologic Characteristics of the Total Study Population (N = 2,749) Stratified Based on Tooth Loss Status (weighted proportions in % [SE]) Clinicopathologic Characteristics of the Total Study Population (N = 2,749) Stratified Based on Tooth Loss Status (weighted proportions in % [SE])



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 $\sum_{i=1}^N\sum_{i$ 

 $4.3(1.0)$ 

Logistic Regression Models With Serum Albumin as a Dependent Variable*‡* (crude OR: 3.15 (95% CI 1.46 to 6.82)



*\** Adjusted for age, sex, and race.

*†* Adjusted for age, sex, race, diabetes status, BMI, CKD status, smoking, denture status, education, and income.

*‡* Tooth loss emerged as a significant predictor of elevated low albumin (Crude OR: 3.15 (95% CI, 1.46 to 6.82) and sustained significance in fully adjusted model 2.

Logistic Regression Analysis With Energy Intake (kcal/kg/day) as a Dependent Variable*‡*



*\** Adjusted for age, sex, and race.

<sup>†</sup><br>Adjusted for age, sex, race, diabetes status, BMI, CKD status, smoking, denture status, education, and income.

*‡* Number of missing teeth was a significant predictor of energy intake in all three models with crude OR: 1.78 (95% CI 1.78 to 2.95)

## Logistic Regression Analysis With Protein Intake as Dependent Variable*‡*



*\** Adjusted for age, sex, and race.

<sup>†</sup><br>Adjusted for age, sex, race, diabetes status, BMI, CKD status, smoking, denture status, education, and income.

*‡* Number of missing teeth remained statistically significant predictor in all regression models after adjusting for all relevant confounders (crude OR: 1.35, 95% CI 1.16 to 2.03)