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Dietary Acid Intake and the Risk of Microalbuminuria in Apparently Healthy Adult Nigerians

Running title: *Dietary acid intake and risk of microalbuminuria*

Abstract

Microalbuminuria is an independent risk factor for cardiovascular diseases (CVD), and it is now considered as an important emerging target for primary prevention strategies in CVD. Restriction of dietary acid intake has been suggested as one possible effective dietary strategy that might offer significant reductions of microalbuminuria. However, reports from previous studies are conflicting. We investigated whether higher dietary acid intake is associated with greater risk of microalbuminuria in apparently healthy adult Nigerians. We assessed dietary intake using a food frequency questionnaire and the Nigerian Food Composition Table. Acid forming potential of our local diets were estimated as Potential Renal Acid Load (PRAL) scores. Urine albumin and creatinine were measured. Microalbuminuria was defined as urinary albumin-creatinine ratio of 30 – 300mg/g. Across the quartiles of the PRAL scores, there was a statistically significant trend with higher intake of dietary acid associated with increased risk of incident microalbuminuria (p for trend < 0.05). We conclude that among the subjects in this study higher intake of dietary acid is associated with significant increased risk of microalbuminuria. We recommend further longitudinal studies that will investigate whether lifestyle modification that include restriction of diet with high acid forming potentials, in the general population or among individuals with cardiovascular risk profile, will be a useful approach in lowering the incidence of microalbuminuria and preventing (and/or delay) cardiovascular diseases in our setting.

Keywords: Dietary acid; Microalbuminuria; Adults; Nigeria

Introduction

Reports from previous studies have established that microalbuminuria is an independent risk factor for cardiovascular diseases (Weir, 2004; Weir, 2007). Microalbuminuria is now known to predict adverse renal and cardiovascular events in diabetic and hypertensive patients, (Weir, 2004; Yuyun et al, 2004; Klausen et al, 2004; Karalliedde et al, 2004; Romundstad et al, 2003 Hillege et al, 2002) and more recent findings show that it is an early marker of future cardiovascular diseases even in healthy subjects (Tanaka et al, 2016). It is an early sign of kidney and cardiovascular end-organ damage, because it reflects subclinical vascular damage in the kidneys and other vascular beds (Weir, 2007; Jensen et al, 1995).

Cardiovascular end-organ damage is one of the leading causes of morbidity and mortality in Nigeria. Moreover, the costs related to the end-organ damage, such as chronic kidney disease and cardiac failure, constitute a significant part of the expenditures in the health care delivery system in Nigeria (Salako et al, 2007; Ulasi et al, 2010; Saidu et al, 2018; Oluwademilade et al, 2020). Therefore, a shift is required from secondary prevention of kidney and cardiac end-organ damage to primary prevention targeting the individuals with an increased risk profile at an early stage.

Because early treatment and modifications of risk factors for microalbuminuria has been found to delay and/or prevent progression to end-organ damage, microalbuminuria is now considered as an important emerging target for the primary prevention strategies (Roscioni et al, 2014; de Zeeuw et al, 2004). Therefore, identifying environmental determinants of albuminuria in our setting might facilitate tailored treatments for the early prevention of cardiovascular end-organ damage and improve the overall cardiovascular risk profile in the general population.

Several approaches to reverse the excessive urinary excretion of albumin have been investigated (Monster et al, 2002; Persson et al, 2016). Recent reports suggest that dietary acid load

restrictions might offer significant reductions of microalbuminuria among diabetic and healthy subjects (Banerjee *et al,* 2014; Ko *et al,* 2017; Kanda et al, 2014; Rebholz *et al,* 2015; Goraya et al, 2012; Kabasawa *et al,* 2019; Banerjee *et al,* 2018). However, the reports are inconsistent and the relation of dietary acid intake with albumin excretion in our setting is largely unknown. Understanding these relations could provide a foundation for a more acceptable, low risk and cost-effective dietary preventive strategy in our setting. Therefore, we undertook a study to investigate whether dietary acid load, which we quantified as potential renal acid load (PRAL), is associated with increased incidence of albuminuria in apparently healthy adult Nigerians.

Materials and Methods

Study population

This was a hospital-based cross-sectional analytical study conducted at the Gombe State Specialist Hospital, Gombe, Nigeria. Two hundred and thirty eight (238) apparently healthy adults volunteers (131 males and 107 females) aged greater than 18 years who gave informed consent were enrolled in to the study. All study subjects were recruited from individuals who presented to the outpatient clinics of the Hospital for routine medical check-up, pre marital screening, blood donors and hospital staff. The study was conducted with the approval of the health research ethics committees of the Gombe State Ministry of Health, Gombe.

The study participants were categorized in to four quartiles according to their median dietary acid intake. Urinary albumin-creatinine ratio (ACR) of 30 – 300mg/g was considered as microalbuminuria (Toto, 2004). Subjects with diagnosed diabetes mellitus or any other illness, those who smoke or ingest alcohol, pregnant and breastfeeding mothers were excluded from the study. Study subjects who were identified as under-reporters or over-reporters of dietary intake (energy intake less than 800kcal/day or greater than 4200 kcal/day respectively) and those on special diets were also excluded from the study.

Data collection

History taking and physical examination were done in each of the subjects in the morning following 10-12 hours of overnight fasting. Data on age, sex and dietary intake were recorded. Body height and weight were taken with each of the study subjects standing erect without shoes or headgear and rounded to the nearest centimeter and 0.1kg respectively. Body mass index (BMI) was calculated as weight in kilogram (kg) divided by height in meters squared (m^2) and

expressed as kg/m^2. Blood pressures (systolic and diastolic) were measured using a mercury sphygmomanometer and expressed in mmHg.

Dietary assessment

Assessment of dietary intake was done using a food frequency questionnaire (FFQ). The FFQ included all the locally available foods as identified by their local names. The FFQ was administered to all the study subjects. Subjects were asked to spontaneously recall all foods and drinks they had consumed over the previous week and to estimate their frequency of consumption and portion size. The frequency of food intakes was then converted to the daily and also the reported portion sizes were converted to grams using household measures.

Where food items were not consumed during the previous week but were part of the usual diet, and for rarely consumed or seasonal foods, frequencies of consumption per month were estimated and converted into frequencies per week. Any food item that is not initially part of the FFQ but is consumed by a subject was added to the list.

Estimation of the daily nutrients and energy intake were estimated by multiplying the frequency of consumption of each food item by its individual nutrients and energy contents in one portion size and then the contributions from all food items consumed were added. Information on the energy and nutrient contents of the food items were obtained from the Nigerian Food Composition Table.

Estimation of Dietary Acid Load

The dietary acid intake for each subject was estimated using the Potential Renal Acid Load (PRAL) score: The Potential Renal Acid Load (PRAL) score was calculated using the following equation (Remer et al, 2003):

PRAL (mEq/day) = 0.4888 × dietary Protein (g/day) + 0.0366 × dietary Phosphorus (mg/day) − 0.0205 × dietary Potassium (mg/day) − 0.0125 × dietary Calcium (mg/day) − 0.0263 × dietary Magnesium (mg/day).

Laboratory analysis

A fresh first-morning spot urine sample was collected from each subject. Albumin level in urine was measured by turbidimetry method (Agappe Diagnostics Limited, India), and urine creatinine level was measured by the Jaffes method (Agappe Diagnostics Limited, India) in the spot urine samples. Fasting venous blood samples were collected in the morning following 10-12 hours overnight fasting into heparin bottles. Blood samples were immediately centrifuged for 15 minutes for separation of plasma, which was stored in aliquots at -20^0C until analysis. Glucose was measured using glucose oxidase method (Agappe Diagnostics Limited, India). All laboratory analyses were done at the Chemical Pathology laboratory of Gombe State University/Federal Teaching Hospital, Gombe.

Statistical analysis

Statistical analysis was done using the Statistical package for social sciences (SPSS) version 20.0. Quantitative data were tested for normality of distribution using the Shapiro-Wilk test and logarithmic transformation was used to improve the normality of distribution of skewed data. Quantitative variables were presented using proportions and measures of central tendency and dispersion. Logistic regression analysis was used to determine the odds ratio of microalbuminuria in the study groups. Kruskall-Wallis test was used to compare the median values of the PRAL scores in the four study groups. Mean differences of energy and selected nutrients intake and urinary albumin excretions were compared across the quartiles of the dietary acid load scores using ANOVA. Partial correlation analyses were used to determine relationship

between dietary acid load scores and urinary albumin excretion and to adjust for confounders. All p-values (two-sided) of less than 0.05 were considered significant.

Results

The demographic characteristics of the study subjects were given in Table 1. Two hundred and thirty eight (238) subjects (55.0% males) with an overall mean age of 33.9 ± 5.3 years were included in the study. The study subjects, whose overall median potential renal acid load (PRAL) score was +9.1mEq/day were further categorized in to four quartiles according to their median dietary acid load scores. The median of the PRAL scores in the first (Q1), second (Q2), third (Q3) and fourth (Q4) quartiles were -23.4mEq/day, +6.1mEq/day, +11.8mEq/day and +45.2mEq/day respectively. The distributions of the subjects in terms of age, sex and body mass index were not significantly different across the quartiles of the PRAL scores (*p for all > 0.05*). Intake of energy and potassium were not significantly different across the quartiles (*p for all > 0.05*). Intakes of dietary phosphorus and protein were higher among subjects in the higher quartiles of PRAL scores (*p for all <0.05*).

The crude and the adjusted odds ratios with 95% confidence intervals for microalbuminuria in the study subjects across the quartiles of PRAL are shown in Table 2. There was an overall 23 (9.6%) incident cases of microalbuminuria among the study subjects. Higher intake of dietary acid was significantly associated with an increased risk of microalbuminuria regardless of gender and independent of age, total energy intake and body weight status (Tables 2 and 3; Figure 1). Across the quartiles, there was a statistically significant trend with higher intake of dietary acid associated with increased risk of incident microalbuminuria (*p for trend < 0.05*).

Table 1: Characteristics of the Study Subjects across the Quartiles of PRAL scores

	Dietary PRAL Scores				
	Q1	**Q2**	**Q3**	**Q4**	***p*-value**
Sample size (n)	60	60	59	59	
Age (years)	33.7 ± 5.4	34.1 ± 5.1	33.9 ± 5.5	34.2 ± 5.7	0.691
Sex ratio	37/23	30/30	37/23	27/31	-
Body Mass Index (kg/m^2)	25.3 ± 3.9	25.0 ± 4.0	24.3 ± 4.2	23.3 ± 5.2	0.705
Systolic BP (mmHg)	119 ± 4.4	118 ± 5.7	118 ± 5.8	117 ± 5.3	0.721
Diastolic BP (mmHg)	79 ± 4.4	79 ± 3.9	79 ± 3.4	78 ± 3.9	0.827
Dietary intakes					
Energy (kcal/day)	2424 ± 300	2441 ± 246	2211 ± 364	1742 ± 542	0.736
Protein (g/day)	78 ± 21	89 ± 7	90 ± 7	108 ± 22	0.000
Calcium (mg/day)	473 ± 190	546 ± 141	536 ± 141	558 ± 127	0.018
Phosphorus (mg/day)	854 ± 217	963 ± 78	977 ± 71	1159 ± 217	0.000
Potassium (mg/day)	3361 ± 759	3293 ± 698	2812 ± 590	2824 ± 607	0.607
Magnesium (mg/day)	1391 ± 194	1081 ± 530	577 ± 620	241 ± 195	0.000
PRAL (mEq/day)*	-23.4	+6.1	+11.8	+45.2	0.000[#]
UAE (mg/g)	22.7 ± 10.3	30.3 ± 14.5	29.8 ± 30.6	64.0 ± 83.0	0.001

m, Mean
SD, Standard deviation
BP, blood pressure
PRAL, potential renal acid load
UAE, urine albumin excretion
Data are presented as ratio or m ± SD.
[*]Median values
[#]Kruskal-Wallis test

Table 2: Odds ratio of Microalbuminuria across the Quartiles of PRAL scores

	Dietary PRAL Scores				
	Q1	Q2	Q3	Q4	
Sample size	60	60	59	59	
		OR (95% CI)	OR (95% CI)	OR (95% CI)	*p-value trend*[#]
Crude	1.0	0.74 (0.16 – 3.44)	0.58 (0.13 – 2.54)	0.23 (0.06 – 0.89)	0.000
Adjusted[*]	1.0	0.63 (0.13 – 2.99)	0.58 (0.13 – 2.54)	0.23 (0.06 – 0.90)	0.000

OR, odds ratio
CI, confidence interval
PRAL, potential renal acid load
[*]adjusted for age and body mass index
[#] obtained from logistic regression analysis
Q1: -23.4, **Q2:** +6.1, **Q3:** +11.8, **Q4:** +45.2

Table 3: Correlation of Urinary Albumin Excretion with the dietary PRAL scores

Variables	All (n=238)		Males (n=131)		Females (n=107)	
	r	***p-value***	***r***	***p-value***	***r***	***p-value***
Age (years)	-0.15	0.022	-0.17	0.050	-0.12	0.221
BMI (kg/m^2)	0.09	0.161	0.11	0.216	0.07	0.457
PRAL score (mEq/day)	0.54	0.000	0.51	0.000	0.58	0.000

BMI, body mass index
r, correlation coefficient
PRAL, potential renal acid load

Discussion

We examined the prevalence of microalbuminuria and its relationship with dietary acid load in a group of apparently healthy adult Nigerians. We reported 9.6% as the overall incidence rate of microalbuminuria among the study subjects and that higher intake of dietary acid was significantly associated with an increased risk of microalbuminuria regardless of gender and independent of age, total energy intake and body weight status.

Several studies conducted in different regions of the world have reported on the prevalence of albuminuria in apparently healthy population; ranging from 4.6% in the general population in Japan to 23.6% among rural population in northern Nigeria (Daviglus *et al,* 2005; Konta *et al,* 2006; Nalado *et al,* 2016; Oluyombo, 2010; Okpere et al, 2012; Jones *et al,* 2002; Ibadin et al, 2004; Correa–Rotter *et al,* 2004; Tanaka et al, 2013). The discrepancy in the wide range of the reported prevalence might be explain by the heterogeneity of the study population, including differences in race/ethnicity, age, gender proportion, body weight status, differences in the assay methods of measuring urine albumin used in the various studies.

We reported a significantly higher risk of microalbuminuria among subjects with higher intake of dietary acid among the study subjects independent of energy intake and body weight status.

Similar findings have been reported in previous studies, where higher intake of dietary acid was shown to be significantly associated with increased risk of microalbuminuria(Banerjee *et al,* 2014; Ko *et al,* 2017; Kanda et al, 2014; Rebholz *et al,* 2015; Goraya et al, 2012). Also in support of the results of this study Kabasawa *et al.* showed that high dietary acid intake is positively associated with increased urinary albumin excretion in subjects with normoalbuminuria (Kabasawa *et al,* 2019). Although Banerjee T et al, reported in a study involving African Americans, that high dietary intake of acid load is associated with increased

incident cases of microalbuminuria, they did not find statistically significant association after adjustment of confounders. The trend of increasing cases of albuminuria across the quartiles of dietary acid load was also not significant (Banerjee et al, 2018).

Variations in sample sizes and heterogeneity of the study subjects, including differences in dietary patterns might explain the inconsistencies in the reports from the various studies. Differences in the methods used in the estimation of dietary acid load might also contribute to the discrepancies.

Several mechanisms by which acidosis could contribute to the increased risk of microalbuminuria have been proposed. High dietary acid load induces the production of ammonium ion [NH_4^+] by the renal tubular cells in order to neutralize the hydrogen ions [H^+] load in the body. Ammonia activates the alternative complement pathway, increases inflammation and tubule-interstitial damage. This produces tubular hypertrophy and glomerular hyper-filtration. Also, as the demand to excrete the excess intratubular [H^+] rises, there is an associated increase in the production of endothelin-1 (ET-1), angiotensin II and aldosterone. Sustained ET-1 levels are associated with increased tubule-interstitial damage, inflammation, and fibrosis, as well as podocyte effacement, together leading to increased glomerular permeability (Wesson et al, 2011; Wesson, 2006; Banerjee *et al,* 2015; Ruíz-Ortega *et al,* 1994; Passey 2017).

Limitations

The study is cross sectional by design; therefore, causality cannot be inferred and there is a possibility of misclassification of risk factors for microalbuminuria such as type 2 diabetes mellitus and hypertension which are defined from single measurements of blood glucose and blood pressure respectively. It was also an observational study, and although we adjusted for

potential confounders associated with both diet content and urinary albumin excretion, residual confounding is still possible and could weaken the strength of association.

Urine Albumin Creatinine ratio was measured only once and this might cause misclassification of microalbuminuria and detailed assessments of other cardiovascular risk factors were also not done.

Conclusion

We conclude that among apparently healthy adult individuals in this study, microalbuminuria is relatively common and higher intake of dietary acid is associated with increased risk of microalbuminuria. This finding may require replication from studies involving larger sample size and various ethnic groups. We recommend further longitudinal studies that will investigate whether lifestyle modification that include reduction/restriction of diet with high acid forming potentials, in the general population or among individuals with cardiovascular risk profile, will be a useful approach in lowering the incidence of microalbuminuria and preventing (and/or delay) cardiovascular diseases in our setting.

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Conflict of interest

Nil

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