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OXIDATIVE BALANCE SCORE AND CHRONIC KIDNEY DISEASE

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Abstract

Background—The Oxidative balance score (OBS) is a composite estimate of the overall pro- and antioxidant exposure status in an individual. The aim of this study was to determine the association between OBS and renal disease.

Methods—Using the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study, OBS was calculated by combining 13 *a priori*-defined pro- and antioxidant factors by using baseline dietary and lifestyle assessment. OBS was divided into quartiles (Q1–Q4) with the lowest, Q1 (predominance of pro-oxidants) as the reference. Multivariable logistic regression and cox proportional hazards models were used to estimate adjusted odds ratios (ORs) for albuminuria defined as urine albumin/creatinine ratio ≥ 30mg/g, macroalbuminuria defined as urine albumin/creatinine ratio >300mg/g and CKD defined as estimated glomerular filtration rate < 60ml/min/1.73m^2 (CKD-EPI) and hazard ratios (HRs) for ESRD, respectively.

Results—Of the 19,461 participants analyzed, 12.9% had albuminuria, 10.1% had CKD at baseline; over a median follow-up of 3.5 years (range 2.14–4.32 years) 0.46% developed ESRD. Higher OBS quartiles were associated with lower prevalence of CKD (OR vs. Q1: Q2=0.93, (95% CI, 0.80–1.08); Q3=0.90, (95% CI, 0.77–1.04); and Q4= 0.79 (95% C.I 0.67–0.92), p for trend <0.01). The associations between OBS and albuminuria (p for trend 0.31) and incident ESRD (p for trend 0.56) were not significant in the fully adjusted models.

Conclusions—These findings suggest that higher OBS is associated with lower prevalence of CKD. Lack of association with ESRD incidence in the multivariable analyses indicates that temporal relation between OBS and renal damage remains unclear.

Keywords

Oxidative balance; pro-oxidant; antioxidant; CKD; ESRD; albuminuria

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The authors have no conflict of interest.

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INTRODUCTION

Oxidative stress has been implicated both in the pathogenesis of chronic kidney disease (CKD) and in cardiovascular complications of CKD such as atherosclerosis [1–4]. Oxidative stress is defined as an imbalance between pro-oxidants and antioxidants in favor of pro-oxidants [5]. CKD is associated with increased levels of reactive oxygen species and nitrogen species (RONS) [5, 6]. This process is observed in early CKD and may contribute to both progressive decline in the glomerular filtration rate and vascular complications [6–8]. Individuals with CKD and compromised nutritional status have more evidence of oxidative stress than well-nourished ones [9, 10].

The balance between pro-oxidants and antioxidants is largely determined by endogenous enzymatic mechanism [11, 12]. However, exogenous factors such as diet, medications and lifestyle are major environmental sources of both antioxidants and pro-oxidants [13]. Ascertaining the individual effects of oxidative balance related exposures is difficult because they are small, may be correlated and there may be existing biological interaction involving pro-oxidant and antioxidant factors [14]. In 2002 Van Hoydonck et al proposed an Oxidative Balance Score (OBS) as a composite measure of oxidative stress-related exposures [15]. OBS uses information about the dietary micronutrient antioxidants and pro-oxidants, antioxidant medication use and pro-oxidative smoking status to summarize pro-oxidant and antioxidant exposure status [15, 16]. Data from population-based studies on pro-oxidant and antioxidant exposure status in individuals with CKD are sparse and focus on individual micro and macronutrients [17, 18] or dietary patterns [19] and their association with outcomes such as end-stage renal disease (ESRD) and mortality.

The OBS has been shown to correlate inversely with all-cause mortality [15], and the risk of sporadic colorectal adenoma [12, 20, 21], and colorectal cancer [22]. However, the associations between OBS and measures of CKD, including estimated glomerular filtration rate (eGFR), albuminuria and incident End Stage Renal Disease (ESRD), have not been previously studied.

SUBJECTS AND METHODS

Study Design

The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study is a national, population-based prospective study to examine reasons for variation in stroke incidence and mortality in the United States. Details on recruitment and data collection were reported previously [23]. Briefly, between January 2003 and October 2007, more than 30,000 healthy volunteers over the age of 45 were randomly selected and recruited with planned equal recruitment of men and women and oversampling of African Americans and residents of the eight southeastern US states because they have higher stroke mortality than the rest of the United States. These states are divided into the “stroke buckle” (coastal plain regions of Georgia, North and South Carolina) and the “stroke belt” (the remaining regions of Georgia, North and South Carolina, Mississippi, Alabama, Tennessee, Louisiana and Arkansas)[19]. Trained personnel collected data by using a computer-assisted telephone survey to obtain socio-demographic factors and other information. Subsequently, a health

professional visited the participants' homes to collect anthropomorphic variables as well as blood and urine samples. At this appointment, a 1998 Block Food Frequency Questionnaire (98-block FFQ; Nutrition Quest, Berkeley, CA) was left with the participant to be self-administered and returned to the data-coordinating center. Various versions of the Block FFQ had been validated in different populations and found to correlate with diet records most correlations being in the 0.5–0.6 range [24]. Although compared to diary entry for nutritional intake, FFQ tend to underestimate micronutrient intake while the total energy intake is overestimated but this measurement error is distributed evenly across study sub-populations [25–27]."

The REGARDS study was approved by the institutional review boards at all the participating centers and all participants provided informed consent.

Participants were then contacted by telephone every 6 months to capture outcomes of interest such as stroke. ESRD status was assessed by linkage with the United States Renal Data System (USRDS). The USRDS is a registry of ESRD, and it captures over 95% of incident cases in the United States [28].

Population

From a total number of 30,239 participants, we excluded 8,686 individuals who did not have data from the block FFQ (28.6%). Of the remaining 21,553, we excluded individuals who were found on record linkage to have already been treated for ESRD (n=23) at the time of baseline interview, those with missing albumin-to-creatinine ratio (ACR) (n=943), then those with missing eGFR (n= 576) and those with missing data on any OBS component (n=550). A total of 19,461 participants were included in the final analysis. Excluded individuals differed only by race and were predominantly black (57.6%).

Oxidative Balance Score

The main exposure (OBS) was calculated by summing up 13 *a priori*-defined pro- and antioxidant exposure factors (table 1) as described previously [13, 15]. These factors include intake of polyunsaturated fatty acid (PUFA), iron, selenium, vitamin C, vitamin E, α carotene, β -carotene, lutein, lycopene, and cryptoxanthine intake; and use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), and alcohol [15]. Smoking was excluded from the original OBS score because smoking is a well-known strong risk factor for CKD [29–34]. A higher OBS is reflective of higher antioxidant levels and low pro-oxidant levels and a lower score is reflective of a lower antioxidant levels and higher pro-oxidant levels. The dietary data were collected at baseline using the FFQ, which consists of 107 items that assesses dietary intake over the previous year. The FFQ has been described in detail in previous studies [19, 35]. Completed questionnaires were scanned and sent to Nutrition Quest ™ (Berkeley, CA) for analysis of nutrition content.

The continuous dietary variables reflecting pro-oxidant (unsaturated fat and iron) and antioxidant (vitamin C, lycopene, α-carotene, β-carotene, lutein, β-cryptoxanthine, vitamin E and selenium) exposures were divided into low, medium, and high categories based on each exposure's sex-specific tertiles. For antioxidants, the first through third tertiles were

assigned 0 through 2 points, respectively, whereas the corresponding point assignment for pro-oxidants was the reverse (0 points for the highest tertile and 2 points for the lowest tertile).

A similar scoring approach was used for pro-oxidant and antioxidant categorical variables. For antioxidant aspirin and NSAID use, 0 points were assigned to participants with no regular use, 1 point to those with unknown or missing data, and 2 points to those with regular use. For pro-oxidant alcohol consumption, non-drinkers, moderate drinkers (1–7 drinks/week for women and 1–14 drinks/week for men), and heavy drinker (>7 drinks/week for women and >14 drinks/week for men) received 2, 1 and 0 points, respectively (table 1).

Outcome Measures

We defined albuminuria as urine albumin/creatinine ratio ≥30mg/g at baseline. Macroalbuminuira was defined as urine albumin/creatinine ratio > 300mg/g. CKD was defined as estimated glomerular filtration rate < 60ml/min calculated by the CKD-EPI equation. The eGFR at baseline was calculated using the CKD-EPI [36] equation using isotope dilution mass spectrometry-calibrated creatinine. Incident ESRD was determined by linkage of the REGARDS study participants to the United States Renal Data System (USRDS) via personal identifiers. ESRD was defined as chronic renal failure requiring permanent renal replacement therapy such as dialysis or transplant [28]t. ESRD status was determined through August 31, 2009.

Covariates

Age, sex, race, smoking, income and educational attainment were self-reported. Region was classified as stroke belt, stroke buckle and other; caloric intake was obtained from the FFQ and analyzed as a continuous variable. We adjusted for systolic blood pressure (sbp), diastolic blood pressure (dbp), baseline eGFR and total cholesterol as continuous variables. Coronary Artery disease (CAD) was defined as History of Heart Disease (self-reported myocardial infarction (MI)), coronary artery bypass, angioplasty, or stenting OR evidence of MI via electrocardiogram.. Diabetes was defined as fasting blood glucose ≥ 126mg/dl, non-fasting blood glucose ≥ 200mg/dl or self-reported use of insulin or oral hypoglycemic agents. Statin use was self-reported. The waist circumference was measured in cm during the in-home visit. Physical activity was assessed by asking how many times participants engaged in intense physical activity enough to work up a sweat (we assessed physical activity as 1–3 times a week and above vs other).

Statistical Analysis

The baseline characteristics of the study population were reported for the overall population and across OBS quartiles. Differences in baseline characteristics between the four OBS quartiles were tested using ANOVA for continuous variables and chi square statistics for categorical variables.

In all analyses the exposure was OBS (in quartiles and as a continuous variable) and the dependent variables of interest were albuminuria, macroalbuminuria CKD and ESRD. The first OBS quartile (predominance of pro-oxidants) was used as the reference group. Odds

ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression for albuminuria and CKD. Adjusted hazard ratios (HR) and 95% CIs were estimated using Cox proportional hazards model for ESRD. We tested the PH assumption by examination of log-log survival curves, Schoenfield residuals, and the extended Cox models and found that the PH assumption was satisfied. The trend tests for OBS (from lower to higher quartiles) in the crude and adjusted models were analyzed by assessing the OBS quartiles as an ordinal variable.

We developed two models to adjust for various confounders based on prior literature review. Model 1 adjusted for age, sex, race, region and calories, and model 2 adjusted for variables in model 1 plus BMI (body mass index), smoking, waist circumference, physical activity, education, income, sbp, dbp, total cholesterol, CAD, diabetes and statin medications. In studying ESRD, we also adjusted for albuminuria and baseline eGFR in addition. All reported p values are two-sided with an alpha of 0.05.

We conducted sensitivity analysis with NSAIDS and aspirin removed from the OBS score and we also investigated the association between the individual components of the OBS score and albuminuria and CKD.

RESULTS

There were 19,461 subjects included in the analyses. Their mean age (SD) was 64.8 (9.2) years, and 55.2% were female and 67.4% were white (Table 2). The mean (SD) OBS was 12.7 (3.7), with median of 13 and interquartile range (IQR) of 10–15. The proportion of white participants was lower in patients with lower vs. higher OBS (Q1=66.3% vs Q4=69.6%).

Higher OBS quartiles (i.e. those with increasing predominance of antioxidants and lower pro-oxidants) included lower proportions of participants in the stroke belt and buckle region. Higher OBS quartiles were associated with lower likelihood of smoking, greater income and education level, and higher likelihood of self-reported hypertension and statin and diabetic medication use.

Table 1 (supplemental) shows the distribution of the individual score components by OBS quartiles. NSAID use was higher in higher vs. lower OBS quartiles. Aspirin use also higher in higher vs lower OBS quartiles. The prevalence of heavy alcohol use was lowest in Q4. The intake of antioxidants (vitamin c, α-carotene, β-carotene, vitamin E, lutein, and lycopene and cryptoxanthine levels) was highest in Q4. However, pro-oxidants polyunsaturated fatty acids and iron were also higher in Q4.

Table 3 shows the crude association between the OBS quartiles and the outcomes: albuminuria, CKD and ESRD. The crude ORs (95% CI) were estimated for CKD and albuminuria and the crude HRs (95% CI) were estimated for ESRD. A total of 2,519 (12.9%) had prevalent albuminuria, 1,957 participants had prevalent CKD (10.0%) and 90 (0.46%) participants developed ESRD over a median follow up period of 3.5 years (range 2.14–4.32 years).). In summary, the crude associations (OR and HR) reflecting the association between OBS quartile and each of the individual outcomes was significant for

macroalbuminuria (p for trend <0.01) but not for albuminuria, CKD or ESRD (table 3). When analyzed as a continuous variable, in the crude model, for every 5-unit increase in the OBS score, the odds of having albuminuria was 0.98 times the odds of not having albuminuria (OR 0.98 95% CI 0.93,1.04) and the odds of having macroalbuminuria was 0.78 times the odds of no macroalbuiminuria (OR 0.78 95% CI 0.68–0.90) (table 4). The results for a 10-unit increase in OBS are also shown in table 3. In the crude model, for every 5-unit increase in OBS, the odds of CKD was 0.99 times the odds of not having CKD (OR 0.99 95% CI 0.93–1.06). For every 5-unit increase in OBS in the crude model, the likelihood of developing ESRD was 0.82 that of not developing ESRD (HR 0.75 95% CI 0.55–1.01). The crude associations between OBS score as a continuous variable and the outcomes (albuminuria, CKD and ESRD) were not statistically significant.

Table 4 shows the associations of OBS with albuminuria, macroalbuminuria, CKD and ESRD, adjusted for various confounders. There was also no significant association between OBS quartile and albuminuria in the fully adjusted model however for macroalbuminuria, compared to Q1, Q3 (OR=0.73, 95% CI 0.55–0.97) and Q4 (OR=0.67, 95% CI 0.49–0.92) were associated with a lower odds of macroalbuminuria (table 4). The trend for macroalbuminuria was also significant for model 1 (p_{trend} <0.01) but not model 2 p_{trend} =0.19) OBS in the highest vs. lowest quartile was associated with significantly lower odds of CKD (OR = 0.83, 95% CI = 0.71–0.96) in model 1. The trend for OBS was also significant for CKD in model 1 (p_{trend}= 0.02). This statistically significant inverse association remained after adjusting for other covariates in model 2 (OR = 0.71, 95% CI = 0.60–0.831). Those in Q4 had a 29% lower odds of having an eGFR <60ml/min. The trend test for OBS in model 2 was also statistically significant (p_{trend} <0.0001).

Using OBS as a continuous variable, for a 5-unit increase in OBS, the odds of having macroalbuminuria was 0.77 times the odds of no macroalbuminuria in model 1 but not significant in model 2. In the crude models, there was no association between the odds of having CKD and a 5-unit increase in OBS score (table 3). However in model 1, (table 4), the odds of having CKD vs no CKD for 5-unit increase in OBS score was 0.93 and this was statistically significant (95% CI= 0.86–0.99). In the fully adjusted model, the odds of having CKD vs no CKD for a 5-unit increase in OBS was 0.90 (95% C.I 0.84–0.97). The association between OBS and ESRD was not statistically significant (table 3 & 4).

A sensitivity analysis excluding NSAIDS and aspirin from the OBS score showed that the association between the OBS and CKD was significant in the crude and adjusted models (p for trend <0.001 in all the models). In addition, Q2 (OR = 0.86, 95% CI = 0.75–1.00) and Q3 OR = 0.71, 95% CI = 0.60–0.83) were associated with significantly lower odds of having CKD. The results were also similar when OBS was analyzed as a continuous variable. (Supplemental table 2)

OBS was significantly associated with albuminuria using linear regression models. A 5-unit increase in OBS was associated with a 7.30mg/g reduction in albuminuria in the crude model (p<0.01), and a reduction of 6.91mg/g reduction in albuminuria (p<0.01). For a 5-unit increase in OBS the eGFR changes by 0.57ml/min (p<0.01) in the crude model and 0.88ml/min in the fully adjusted model p<0.001) (supplemental table 3)

When we investigated the crude association between albuminuria and the individual pro and anti-oxidant we found that unsaturated fats ($p<0.01$), iron ($p<0.01$), a-carotene ($p<0.0001$), lutein ($p<0.01$), NSAIDS ($p<0.05$), smoking ($p<0.0001$), selenium ($p<0.05$), aspirin ($p<0.0001$) and alcohol ($p<0.0001$) (supplemental table 4).

The crude analysis of the association between pro and anti-oxidant factors and CKD, showed that unsaturated fat ($p<0.0001$), iron ($p<0.05$), lycopene ($p<0.01$), a-carotene ($p<0.001$), b-carotene ($p<0.0001$), lutein ($p<0.0001$), b-cryptoxanthine ($p<0.01$), a-tocopherol ($p<0.0001$), smoking ($p<0.001$), aspirin ($p<0.0001$) and alcohol ($p<0.001$) were all individually associated with CKD (supplemental table 4).

DISCUSSION

We examined the association between OBS, albuminuria, CKD and ESRD and found that higher OBS quartiles (which reflect an increased antioxidant effect) were associated with lower prevalence of CKD, as measured by eGFR < 60ml/min/1.73 m^2 and associated with albuminuria in the linear regression models and macroalbuminuria in the crude and partially adjusted models but not associated incident ESRD.

Our study suggests that the greater the shift from pro-oxidant to antioxidant exposures (as measured my higher OBS), the lower the odds of CKD as defined by an eGFR<60ml/min. To our knowledge, this is the first study that utilizes the OBS to determine the association between the balance of pro-oxidant and antioxidant exposure and kidney disease.

The lack of association between OBS and incident ESRD are inconclusive due to the small number of participants that developed ESRD and the relatively short follow-up period. This warrants further investigation into the association between OBS and ESRD when there is longer follow-up data available. Other possible explanations of this are that since the FFQ is measured at baseline, secular dietary changes, particularly those that may occur among participants with prevalent CKD who have many dietary restrictions, are not accounted for. It also suggests that the temporal association between OBS and renal damage remains unclear.

There was a significant inverse association between OBS and CKD as defined by eGFR< 60ml/min that became more pronounced as we adjusted for potential confounders. Current evidence suggests that CKD is a pro-oxidant state as evidenced by the increase in oxidative markers in atherosclerotic lesions of patients with CKD as well as in circulating plasma of CKD patients [37–39]. Our results suggest that the OBS score may be a measure of pro- and antioxidant exposure in CKD. Measuring the OBS may be the first step in detecting pro-and antioxidant exposure in individuals at risk for development of an eGFR< 60ml/min. These results need to be further validated using incident CKD cases in a dedicated CKD cohort.

OBS has been validated in previous studies. Kong et al validated the OBS in all-cause, cancer and non-cancer mortality in the REGARDS cohort [40]. Dash et al also validated the OBS in a pooled Case-Control Study of incident, sporadic colorectal adenoma [21]. OBS was also found to be associated with circulating biomarkers of oxidative stress F2-isoprostanes and C-reactive protein in colorectal adenoma [41].

The strengths of the study include that we utilized a large population cohort. The OBS provides a measure whereby the effects of pro- and antioxidant factors in the diet and medications are summed up and this “effect” or “balance” can be used to determine outcomes. The *a priori* selection of cut-offs in the components of OBS reduces subjectivity in measurement [12].

The limitations of the study include the small number of incident ESRD cases in the cohort; misclassification due to self-reported data, particularly dietary assessments from the food frequency questionnaire, to determine the OBS. Although dietary questionnaires are prone to recall bias due and nutritional intake recorded may be inaccurate, on the population level, they provide a satisfactory classification of nutrient intake [27, 42, 43].The study of CKD and albuminuria was cross-sectional; selection bias from missing data; and residual confounding. The OBS was limited to dietary/lifestyle exposures and included no endogenous measures of antioxidant cell function [44, 45].

The goal of identifying the individuals at risk for higher oxidative stress is to institute aggressive risk modification. This study suggests that higher OBS may be independently associated with lower prevalence of CKD and may represent a modifiable risk factor for CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

OXIDATIVE BALANCE SCORE (OBS) COMPONENTS[a]

1. Cryptoxanthine	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
2. Selenium supplements	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
3. Aspirin	0 = never, 1 = missing, 2 = current user
4. Other NSAID[b]	0 = never, 1 = missing, 2 = current user
5. Alcohol Female	0 = 8+ drinks/week, 1 = 1–7 drinks/week, 2 = <1 drink/week
Male	0 =15+ drinks/week,1 = 1–14 drinks/week, 2 =<1 drink/week
6. PUFA[b]	0 = high (3rd tertile), 1 = medium (2nd tertile), 2 = low (1st tertile)
7. Total (dietary and supplemental) iron	0 = high (3rd tertile), 1 = medium (2nd tertile), 2 = low (1st tertile)
8. Total (dietary and supplemental) vit. C	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
9. Total (dietary and supplemental) α-carotene	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
10. Total (dietary and supplemental) β -carotene	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
11. Total (dietary and supplemental) vit E.	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
12. Lutein	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)
13. Lycopene	0 = low (1st tertile), 1 = medium (2nd tertile); 2 = high (3rd tertile)

[a] Low, medium and high categories correspond to sex-specific 1st, 2nd, and 3rd tertiles

[b] NSAID = non-steroidal anti-inflammatory drug (not including aspirin); PUFA = polyunsaturated fatty acid

Table 2

CHARACTERISTICS OF PARTICIPANTS IN THE REGARDS COHORT BY OBS QUARTILES AT BASELINE. (HIGHER QUARTILES REPRESENT HIGHER ANTIOXIDANT EXPOSURE)

Characteristic	All	OBS Quartile			
		Q1	Q2	Q3	Q4
OBS Range	2–24	2–9	10–12	13–15	16–24
N	19462	4096	5090	5453	4823
Age (SD)	64.8 (9.2)	63.5 (9.3)	64.4 (9.3)	65.2 (9.1)	65.9 (8.9)*
Female	55.2	55.1	55.1	55.4	55.3
White	67.4	66.3	66.4	67.3	69.6*
Current Smoking	13.5	19.9	15.2	11.1	9.0*
Income less than $20k	15.2	16.7	15.3	15.3	13.8*
Education < high school	9.3	11.6	10.2	8.9	7.1*
HTN	56.3	52.9	55.9	56.9	58.7*
DM	17.8	17.3	17.3	18.4	18.0
Waist circumference (cm)	57.8	56.9	58.3	57.7	58.4
BMI (kg/m^2)	30.0 (6.0)	28.7 (5.9)	29.0 (6.1)	28.9 (5.9)	29.2 (6.0)
Calories (Kcal)	1709 (709)	1436 (573)	1610 (654)	1767 (702)	1981 (766)*
eGFR ml/min/1.73m^2	85.2 (18.8)	87.8 (19.5)	85.3 (19.2)	84.9 (18.6)	84.9 (17.9)
ACR (mg/g)	39.7 (234.8)	49.8(320)	42.1 (237)	37.4 (210)	31.3 (159)*
OBS mean (SD)	12.7 (3.7)	7.6 (1.4)	11.0 (0.81)	14.0 (0.82)	17.5 (1.5)*

BMI Body Mass Index; eGFR creatinine estimated glomerular filtration rate; ACR albumin-to-creatinine ratio; OBS oxidative balance score.

†Values for age, BMI, calories, hemoglobin, eGFR, ACR and OBS years are reported as mean (±SD). Race, sex, current smoking status, income, education, hypertension (HTN), diabetes (DM and waist circumference are reported as percent.

*p<0.001 based on the ANOVA for continuous variables and chi-square (X^2) test for categorical variables.

Table 3

CRUDE MODELS SHOWING THE ASSOCIATION BETWEEN OBS: ALBUMINURIA CKD AND ESRD

		Albuminuria		Macroalbuminuria		CKD		ESRD			
OBS	**Total (N)**	**Cases N (%)***	**OR (95%CI)**	**Cases N (%)**	**OR (95%CI)**	**Cases N (%)***	**OR (95% CI)**	**Total PY**	**Cases**	**IR****	**HR(95% CI)**
Q1	4096	536 (13.1)	1	104(0.53)	1	410(10)	1	12968.5	20	1.54	1
Q2	5090	667(13.1)	1.0(0.88–1.13)	117(0.6)	0.90(0.69,1.17)	519(10.2)	1.02(0.89–1.17)	16488.6	28	1.70	1.2(0.67–2.16)
Q3	5452	704(12.9)	0.99(0.87–1.11)	111(0.57)	0.67(0.51,0.88)	566(10.4)	1.04(0.91–1.19)	17851.5	25	1.40	0.93(0.51–1.71)
Q4	4823	611(12.7)	0.96(0.85–1.09)	78(0.4)	0.72(0.54,0.97)	462(9.6)	0.95(0.83–1.10)	16111.4	17	1.06	0.72(0.37–1.38)
p for trend			0.51		0.0047		0.55				0.21
OBS# (continuous)											
5-unit			0.98(0.93–1.04)		0.78(0.68,0.90)		0.99(0.93–1.06)				0.82(0.621.08)
10-unit			0.96(0.86–1.08)		0.61(0.46,0.81)		0.99(0.87–1.12)				0.67(0.38–1.17)
P value			0.51		0.0007		0.85				0.15

OBS = oxidative balance score; OBS#=OBS continuous, OR = odds ratio, HR = hazards ratio; CI= 95% confidence interval. *% = Percentage of the entire quartile with the outcome PY= person years **IR = incident rate per 1000 person-years, CKD= Chronic Kidney disease. ESRD= End Stage renal disease.

Logistic regression was used to calculate odds ratio for Albuminuria and CKD while Cox proportional hazards models were used to calculate hazard ratios for ESRD.

Table 4

MULTIVARIABLE MODEL SHOWING ADJUSTED ASSOCIATION BETWEEN OBS: ALBUMINURIA, CKD, AND ESRD

OBS	Macroalbuminuria[a]		Albuminuria[a]		CKD[a]		ESRD[b]	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	OR (95%CI)	OR(95% CI)	OR (95%CI)	OR(95% CI)	OR(95% CI)	OR (95% CI)	HR(95% CI)	HR(95%CI)
Q1	1	1	1	1	1	1	1	1
Q2	0.85(0.66,1.11)	0.88(0.67,1.14)	0.96(0.85,1.09)	1.00(0.88, 1.14)	0.95(0.82,1.09)	0.93(0.80,1.08)	1.21(0.67,2.18)	1.81(0.93, 3.50)
Q3	0.70(0.54,0.92)	0.73(0.55,0.97)	0.92(0.84,1.04)	0.97(0.85, 1.11)	0.93(0.80,1.07)	0.90(0.77,1.04)	0.99(0.53,1.83)	1.99(0.997,3.97)
Q4	0.65(0.49,0.88)	0.67(0.49,0.92)	0.89(0.77,1.01)	0.95(0.82, 1.09)	0.83(0.71,0.96)	0.79(0.67,0.92)	0.85(0.43,1.68)	1.17(0.52,2.65)
p for trend	0.0017	0.0053	0.05	0.36	0.02	<0.01	0.50	0.67
OBS (continuous)								
5-unit	0.83(0.72,0.95)	0.83(0.72,0.96)	0.94(0.89,1.00)	0.97(0.91, 1.03)	0.93(0.86,0.99)	0.90(0.84,0.97)	0.88(0.65,1.19)	1.08(0.78, 1.50)
10-unit	0.68(0.52,0.90)	0.68(0.51,0.91)	0.89(0.76,1.00)	0.93(0.82, 1.06)	0.86(0.74,0.99)	0.81(0.70,0.94)	0.78(0.42,1.43)	1.17(0.61, 2.25)

[a], For Macroalbuminuria, Albuminuria, and CKD, model 1 is the crude model model 2 is adjusted for age, sex, race, region and calories;

[b], For ESRD, model 1 is adjusted for age, sex, race, region and calories; model 2 is adjusted for age, sex, race, region and calories, BMI (body mass index), smoking, waist circumference, physical activity, education, income, diabetes, statin medications, cardiovascular disease, systolic and diastolic blood pressure, and Total Cholesterol.

OBS=oxidative balance score; OBS# = OBS as a continuous variable, HR=hazards ratio; CI= 95% confidence interval. **IR = incident rate per 100,000 person-years.

Logistic regression was used to calculate odds ratio (OR) for Albuminuria and CKD while cox proportional hazard was used to calculate hazard ratios for ESRD. Model 1 adjusted for age, sex, race, region and calories. Model 2 adjusted for variables in model 1 plus BMI (body mass index), smoking, waist circumference, physical activity, education, income, spb, dpb, cholesterol, CAD, diabetes and statin medications. Model 3 adjusted for variables in model 1 and baseline eGFR and albumin/creatinine ratio.