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Article

Association between vitamin C deficiency and metabolic syndrome among patients with kidney disease: An evidence from NHANES 2007-2008 data

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Abstract：

Introduction: Elevated albuminuria is an important outcome of diabetic complications and metabolic syndrome (MetS), the complex metabolic abnormalities manifested as glucose intolerance, hypertension, and dyslipidemia, and enlarged waist circumference. Cardio-metabolic abnormalities are also associated with oxidative stress and low-grade inflammation. Vitamin C (Vit C) has long been recognized as a hydrophilic antioxidant and blocker of oxidative stress which also has a protective role of MetS and kidney disease. **Objective**: This study aimed to identify the predictive effect of its deficiency on kidney disease among patients who developed metabolic syndrome. **Method and procedures**: To meet this objective, the National Health and Nutrition Examination Survey (NHANES) 2007-2008 data were used. NHANES represents the civilian, non-institutionalized United States population data implemented for a continuous system of monitoring health, nutritional status, and well-being in the US. The predictive power of MetS on Albumin Urea (AU) and vitC deficiency (vitC < 0.25 mg/dl) as effect modifiers were assessed using a binary logistic regression. Age, gender, race, and BMI were used as covariates. **Results**: Among the respondents, 1.9% of the US population had the risk of kidney damage, whereas 14.5 % of respondents had MetS. MetS were significantly and positively correlated with AU ($p < 0.01$). A higher elevation of albuminuria creatinine ratio (ACR) was found in participants with VCD. The logistic regression models estimated in this study showed that the severity of kidney disease, measured by ACR, was increased for individuals who developed both VCD and MetS as compared with individuals who developed MetS only (AOR=5.53; 95% CI: 2.73, 11.21). An increase in age and being African-American were found to be associated with an elevated AU. **Conclusion**: The study demonstrates that vitamin C deficiency mediates the risk of developing kidney disease among patients with MetS. Being old age and African-American individuals are associated with kidney disease. So that, vitC fortified foods on prevention of kidney diseases among patients with MetS needs to be considered for patients with MetS. Moreover, there is a need to call for the concerned bodies to give special attention to African-American and old age individuals to prevent the complication of MetS into kidney disease.

Keywords: Metabolic syndrome; vitamin C deficiency; kidney disease; Albuminuria; USA

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1. Introduction

Kidney disease has recently become a critical public health problem, accounting for the ninth cause of death in the United States (US) affecting about 20 million Americans [1]. In the US, approximately 6% of men and 9.7% of women have albuminuria [2]. Albuminuria (AU), defined as the excretion of over 30 mg/g urinary albumin creatinine ratio, is known to be the most basic indicator of kidney impairment and is a tool for early detection of diabetic nephropathy [3]. AU is an important extrapolative factor for the progress and complications of diabetes and the related adverse events in patients with type I and types II DM and blood pressure (BP) [4]. Though the mechanism is not fully understood, chronic kidney disease (CKD) is associated with cardiovascular disease (CVD). Recent clinical trials based on morning spot urine tests showed that albuminuria predicts mortality from cardiovascular, renal, and all other causes of mortality better than those of glucose status and BP [7].

Glucose intolerance, hypertension, dyslipidemia, and large waist circumference constitute the so-called metabolic syndrome (MetS[8]. These factors are all linked to an increased risk of insulin resistance, diabetes, kidney disease, and cardiovascular disease [9, 10]. MetS are associated with elevated albuminuria [11], directly or indirectly through insulin resistance, increased pro-inflammatory cytokines, and reduced anti-inflammatory cytokines [12]. Reduced hemodynamic dysfunction of insulin and bioavailability of nitric oxide affects the vasculature leading to endothelial dysfunction [13], and aggravated Insulin Resistance (IR). IR may result from inflammation-induced insulin resistance, namely inhibition of the PI3K-Akt pathway subsequently leading to reduced Akt phosphorylation and glucose uptake, glycogen, or fat synthesis [13, 14].

Targeting oxidative stress and inflammation as a means of preventive or treatment options in conjunction with hypoglycemic agents may be beneficial. This is because of a reactive oxygen species with oxidative stress that leads to cellular death of the vital organs [15]. For this, ascorbic acid (vitC) has a powerful antioxidant scavenging free radicals such as hydroxyl radical and singleton oxygen [16] that may damage the renal tissue [15]. There is also strong evidence that giving oxidized and reduced vitamin C is potent to protect aged kidney tissue as investigated under animals' study[17].

So, the primary purpose of this study was to determine the predictive effect of MetS on AU and how this is provoked by the presence of vitC deficiency (VCD). We assumed that MetS predict AU and vitC deficiency may deteriorate the advancement of kidney disease. Age, gender, race, and BMI were used as covariates to adjust for potential confounding.

2. Methods and Procedures

2.1. Study design, area, and period

A survey-based cross-sectional study design was conducted in the United States of America from January 2007 - December 2008

2.2. Source and study population

This study was conducted among the civilian, non-institutionalized US population. The NHANES 2007-2008 data were used to examine the association of metabolic syndrome and kidney disease assessed by urinary albumin excretion.

2.3. Eligibility criteria, Sampling technique, and procedures

The NHANES survey design was a stratified, multistage probability sample of the civilian non-institutionalized United States population. The stages of sample selection were: (1) selection of Primary Sampling Units (PSUs) which were counties or small groups of contiguous counties, (2) segments within PSUs (a block or group of blocks containing a cluster of household), (3) households within segments, and (4) one or more participants within households. A total of 15 PSUs were visited for 12 months. In 2007-2008 a new sampling methodology was implemented. All Hispanics were oversampled, not just Mexican Americans. Besides, for each of the race/ethnicity domains, the 12-15 and 16-19 year age domains were combined and the 40-59 year age minority

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domains were split into 10-year age domains of 40-49 and 50-59. This has led to an increase in the number of participants aged 40 and older and a decrease in 12 to 19-year-olds from previous cycles. Lastly, pregnant women are no longer oversampled. Based on these changes, some variables have been modified from previous release cycles. The surveys examine a nationally representative sample of approximately 5,000 persons each year. These persons were located in counties across the United States, 15 of which are visited each year [18]. 2.4. Data collection methods and Laboratory Analyses

Modes of data collection include audio computer-assisted self-interview (ACASI), computer-assisted personal interview (CAPI), computer-assisted self-interview (CASI), face-to-face interview, and on-site questionnaire. Vitamin C was measured as serum ascorbic acid, an indicator of tissue stores [19] by isocratic High-Performance Liquid Chromatography (HPLC) with electrochemical detection at 650 mV. Laboratory analysis of urinary albumin followed the procedure of Chavers et al using a non-competitive, double-antibody solid-phase fluorescent immunoassay [20]. The first antibody to human albumin was covalently attached to derivatized polyacrylamide beads, this was reacted with a urine specimen and the urine albumin-antigen complexes were further reacted with the second fluorescein-labeled antibody. The fluorescence level was determined within the functional range of 0.5–20 μg/mL of albumin. Data were corrected for creatinine determined from the same specimen. Creatinine, the waste product derived from creatine, is released into the plasma at a relatively constant rate assuming that the amount of creatinine per unit of muscle mass is constant. Creatinine is also an indicator of impaired kidney function. Creatinine analysis is based on reaction rate measurements with picrate in an alkaline solution to form a red creatinine-picrate complex at two wavelengths 520 and 560 nm according to established protocols of Creatinine Measurement Module Operating and Service Instructions, Beckman ASTRA. Brea (CA).

2.5. Study variables and operational definitions

Metabolic syndrome (MetS) was defined according to the latest definition of ATP III from the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) and the 2009 Joint Scientific Statement [8]. Data files were combined using SPSS; the variable MetS was created according to the standard definition that 3 out of 5 risk factors were used to determine metabolic syndrome (MetS) [21-23]: 1) Waist circumference (WC) ≥ 102 cm (males adults) and ≥ 88 cm (female adults); 2) FG ≥ 100 mg/dl; 3) BP ≥ 130/85 mm Hg (either); 4) TG ≥ 150 mg/dl; and 5) HDL <40 mg/dl (male adults) and <50 mg/dl (female adults). WC was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm. Serum TG concentrations were determined with the enzymatic hydrolyzation to glycerol. HDL was determined by the lipoprotein precipitation method using heparin–manganese chloride. FBG (Fasting Blood Glucose) was determined by the standard enzymatic method. The average of all available BP measurements was used in this study.

Variables were computed both in the form of continuous or categorical values. When categorized, conventional literature values were used. The following cut-off points were used for the different variables: Urinary albumin: creatinine ratio (ACR) above 30 mg/g was defined as albuminuria (AU). In this paper, ACR was used to represent the continuous variable, and AU was used to represent the categorical variable. In this study, Low serum vitamin C is defined as less than 0.25 mg/dl; unpublished data from the second National Health and Nutrition Examination Survey of the US population from 1976-1980.

2.6. Data quality, processing, and analysis

Data were sorted and checked for its quality and then analyzed using SPSS (Statistical Package for Social sciences version 24, IBM, Armonk, NY, USA) software. Descriptive statistics included mean comparisons, t-tests, and ANOVA for continuous, normally distributed variables, and proportions and Chi-squared tests for ordinal and nominal variables. Binary logistic regression was fitted to assess the strength of association between the dependent variable AU and the independent

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variable MetS. The association of ACR with vitC status was first determined using different statistical methods such as independent t-test, one-way ANOVA, and correlation matrix. VCD was identified as an effect modifier through statistical computations of binary logistic regression before and after adjusting for, without, and with consideration of the interaction terms. Covariates considered to be potential confounders were included such as age groups, gender, BMI (Underweight, normal and overweight), and race/ethnicity stratified into three groups (White, African American, Others). The crude and adjusted odds ratios together with their corresponding standard errors were computed. A p-value less than or equal to 0.05 was considered statistically significant.

2.7. Ethics approval and consent to participate

Initially, the study was exempted by the Internal Review Board of Wayne State University. All respondents provided their informed consent, and the NHANES protocol was reviewed and approved by the NCHS Research Ethics Review Board. Beyond this, currently, the data used in this study are de-identified public data available for secondary analysis. Before data collection, informed written consent was obtained from the study participants after a detailed explanation about the purpose and importance of this study. For minors, especially for the study participants whose age was less than 18 years old, informed assent was also undertaken. The detailed survey procedures including Ethical approval, human subject consent, home or mobile center examinations, interviews, and blood collections, are already available elsewhere [24]. Moreover, the authors confirmed that the NHNES-2007-2008 investigations were carried out following the rules of the Declaration of Helsinki of 1975. The overall ethical code regarding the NHANES 2007-2008 data is already available at:
https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Documents.aspx?BeginYear=2007

2.8. Availability of data and material

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

3. Results

A total sample of 10,348 from NHANES 2007-2008 was included in the analysis. The proportion of female participants was 50.9 % compared to men (49.1%). The mean age of male participants was 28.06 years with a standard error of 0.34 years (N=5,080) and 27.9 years for female participants (N=5,268). With regard to race distribution, 2,710 (26.2%) were African Americans; 3,928 (38.0%) were White, and 3,710 (35.9 %) were others (**Table 1**). The result of this study showed that a total of 1,140 (11%) of 8954 participants had MetS showing 3 or more risk factors for MetS. The remaining 3785 (36.6%) of participants had 1 or 2 components of MetS and 4029 (38.9%) had no MetS.

Table 1. Socio-demographic characteristics of the US population; data from NHANES 2007-2008.

Variables	Characteristics	No (%)
Gender	Male	5080 (49.1)
	Female	5268(50.9)
Age in years	<20	5369(51.9)
	20-39.9	1923(18.6)
	40-59.9	1486(14.4)
	≥60	1570(15.2)
Race	African-American	2710(26.2)
	American-Whites	3928(38.0)

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Others	3710(35.9)

NB; others mean Mexican American, other Hispanics, or mixed races.

3.1. Health and morbidity characteristics

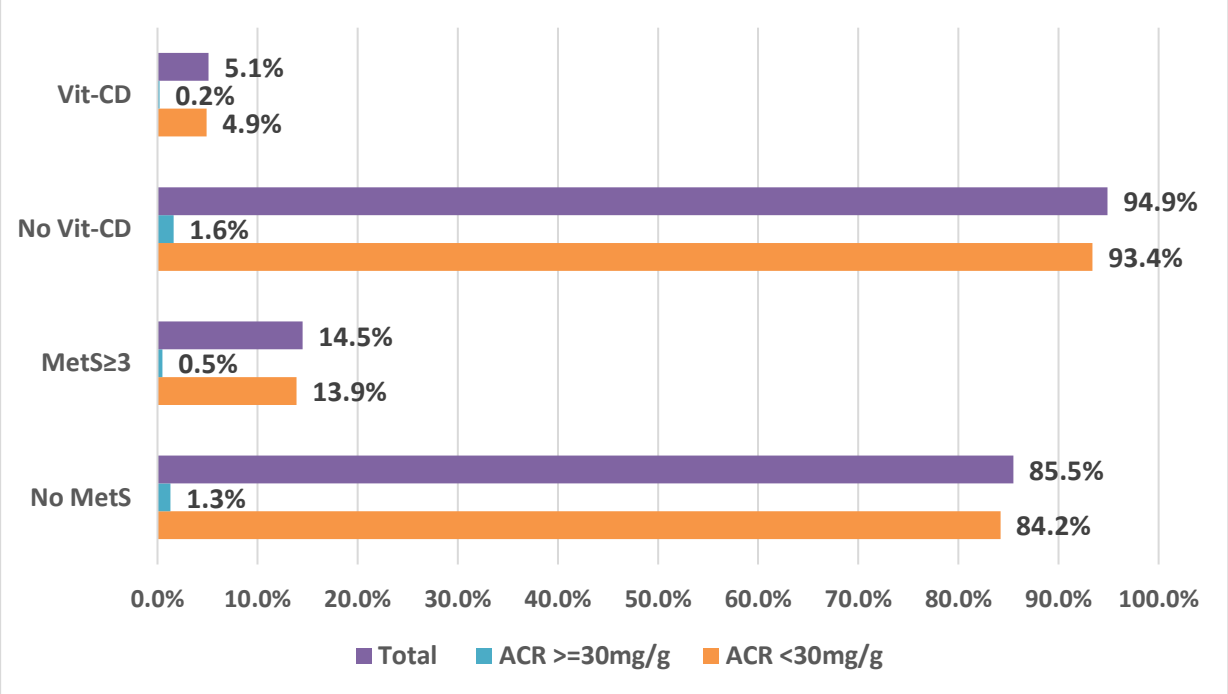
The NHANES 2007-2008 data of the US population showed that 3.7% of women were pregnant and 40% of the population was overweight/obese (BMI >= 25kg/m^2). Among the study participants, Vit-D deficiency and T2diabetes Mellitus were 33.1% and 5.0%, respectively (**Table 2)**.

Table 2. Health and morbidity characteristics of US Population-based on NHANES 2007-2008.

Variables	Frequency	Percent
Pregnancy status(n= 3371)		
Yes	382	11.33
No	2791	82.80
Uncertain	200	5.93
BMI(n=8880)		
Underweight (<18.5Kg/m^2)	1892	21.3
Normal (18.5 -24.9kg/m^2)	2838	31.96
Overwt/obese(>= 25kg/m^2)	4150	46.73
Vit-D (n=8306)		
No VitDD (VitD≥ 20 ng/ml)	4880	58.75
VitDD(VitD < 20ng/ml)	3426	41.23
T2Diabetes status(n=9813)		
No T2DM	9292	94.7
T2DM	521	5.3

3.2. Prevalence of Kidney Disease, Vitamin C deficiency, and metabolic syndrome

Based on the survey, the percentages of the US population who had the risk of kidney damage and developed metabolic syndrome (MetS≥3) are 1.9% (N=145) and 14.5% (N=1132), respectively. Besides, 5.1% (N=366) of the population was Vitamin C deficient as shown below (**fig.1**).



NB; Vit-CD= Vitamin C deficiency, MetS= Metabolic Syndrome, ACR=Albumin Creatinine Ratio

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Figure 1. Prevalence of kidney disease, metabolic syndrome, and relation with Vit-C deficiency in the US population from NHANES 2007-2008.

3.3. The association between vitamin C deficiency and metabolic syndrome

Collinearity diagnosis was carried out using the variance inflation factor (VIF) and the tolerance value, which was found to be acceptable for continuous variables [25]. From the output, the following equation was established as ACR=6.037-1.92* vitamin C+ 0.76. This implies that for a unit decrease in serum vitamin C, the risk of developing kidney disease can be increased nearly by two folds (coefficient =-1.92; 95% CI:-3.41,-0.43) though it explained only 0.1 percent compared with the other un-explained variables (R^2=0.001 and p value<0.01).

The binary logistic regression analysis was also undertaken to determine the strength of association between the outcome variable AU and the predictor variable MetS and the effect modifier VCD (**Table 3**). Keeping other variables constant, the risk of elevated AU was significantly associated with MetS, having more than two folds (COR= 2.55; 95% CI: 1.76, 3.66) as compared with individuals who had normal AU. By adjusting for VCD alone, the odds ratio slightly increased (AOR=2.63; 95% CI (1.80, 3.85). After including an interaction term the adjusted odds ratio was reduced (AOR=2.43; 95% CI: 1.61, 3.66). The severity of kidney disease measured by ACR was increased among individuals who developed both VCD and MetS (AOR=5.53; 95% CI: 2.73, 11.21), indicating that vitC was an effect modifier between MetS and ACR.

Moreover, the following equations were developed from regression analyses after data weighting:

$$AU=-4.12+ 0.94 \times MetS \text{ (crude)} \quad (1)$$

$$AU=-4.31+ 0.97\times MetS + 0.69 \times VCD \quad (2)$$

$$AU=-4.28 + 0.89 \times MetS \text{ (with VCD)} \quad (3)$$

$$AU=-4.23 + 0.87 MetS \text{ (without VCD)} \quad (4)$$

$$AU=-4.08+1.71\times MetS*VCD \quad (5)$$

Equation 1 shows that MetS was a risk for AU regardless of potential effect modifiers or confounders (p<0.001). Results from Equation 2 (see Table 2) show significant effects of MetS and VDD on AU (p<0.01). Equations 3 and 4 calculate the effect of MetS on AU accounting for the interaction with VCD. Computing the odds ratios from these coefficients ($e^{0.89}$ (OR=2.43) for MetS effect on AU in the presence of VCD vs. $e^{0.87}$ (OR=2.38) in the absence of VCD), the effect of MetS on AU was high among individuals who developed VitC deficiency compared with their counterparts.

Regardless of other covariates, VCD showed an increased risk of AU. About 20-29.9, participants, ages greater than or equal to 60 years had increased odds of developing AU (p<0.001). The odds of AU increased with the increasing age range. Higher age ranges had positive predictive power on AU. Whereas the predictive power of race was generally high among African-Americans.

Table 3. Binary logistic regression analysis indicated the strength of the association between the predictor variables and ACR.

Variables	Model 1: Bi-variable analysis	Model 2: VCD	MetS*VCD	Model 3: race, gender & age
MetS	[1.76,3.66]	[1.80,3.85]	[1.61,3.66]	[1.24,1.87]
(>=3)	**2.55*****	**2.63*****	**2.43****	**1.89****
VCD	[1.35,4.20]	[1. 14,3.59]	[0.48,2.90]	[1.20,3.89]
(<0.25 mg/dl)	**2.38****	**2.03***	**1.18**^{x}	**2.16***
Race	[0.99,2.17]			[1.17,2.81]
(African -American)	**1.46**$^{\wedge}$			**1.81****

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Gender (Female)	[0.82,1.58] **1.14**^{x}	[0.87,1.79] **1.25**^{x}
Age (>=60 years)	[2.67,7.69] **4.53*****	[2.20,7.06] **3.94*****
MetS*VCD	[2.73,11.21] **5.53****	
BMI	[0.92,2.00] **1.36**^{x}	[0.51,1.86] **1.12**^{x}

Odds ratios reported; ^{x}p>0.20, $^{\wedge}$p< 0.20, *p< 0.05, **p< 0.01, ***p< 0.001.

4. Discussion

In this study, we indicated that there is a positive association between MetS and AU worsened by VCD. We hypothesized that MetS predict AU and this association is significantly aggravated by VCD. It was evident from this study that the MetS and VCD interact in worsening the risk of AU as a measure of kidney disease. The association of MetS with AU remained significant after adjusting for VCD as an effect modifier and other potential confounders including body mass index (BMI) as a measure of adiposity, though it had an insignificant relationship with ACR. Moreover, in the final regression analysis, we also considered potential confounders such as age, gender, and race. African Americans were at higher risk of developing metabolic abnormalities and the risk of kidney disease measured by ACR as compared with the white race. Moreover, old age individuals had also an increased risk of developing kidney disease as compared with early adulthoods.

Even though the relationship between MetS and kidney disease is biologically plausible [26], the pathophysiology of how MetS cause kidney disease was not fully understood. However visceral adiposity with adipose tissue expansion as a component of measuring MetS is highly interrelated with insulin resistance [27]. Insulin resistance is becoming the non-traditional risk factor in the causal pathway of kidney disease [28]. Insulin resistance is also associated with endothelial dysfunction, reduced synthase of endothelial nitric oxide, and worsening of renal hemodynamic function in conjunction with an injury of podocytes resulting in hypertension and albuminuria [29]. Moreover, insulin resistance is associated with sodium retention, overproduction of low-density lipoprotein cholesterol, and hypertriglyceridemia, which may impair mitochondrial function and promote kidney cell damage [30].

However, it is the interest of the authors to warrant further investigation about the role of metabolic syndrome on the incidence and progression of kidney disease.

From this study, we evidenced that vitamin C deficiency (<0.25 mg/dl) worsens kidney disease among individuals who already developed metabolic syndrome. This hydrophilic antioxidant and specific cofactor for enzymes[31] had more effect on waist circumference and triglyceride which in turn improves the lives of patients with MetS[32]. Vitamin C is also associated with an increased risk of endothelial dysfunction via an increase in oxidative stress among non-diabetic chronic kidney disease patients[33]. Animal studies also reported that vitC supplementation may maintain kidney morphology, renal function, and decrease albuminuria[34] through the blockage of oxidative stress[35]. However, the exact biological mechanism of how vitC worsens kidney disease among patients with MetS warrants further exploration.

Identification of the covariates while establishing the relationship between MetS and Kidney disease was also the interest of this study. Astonishingly, BMI was not significantly associated with ACR. However, linear measurement of body parts and other crude measurements like that of BMI may not indicate the cause and effect relationship between the body fat accretion and the different cardio-metabolic syndromes [36]. Hence utilization of the standardized tools which may report the true body fat distribution had paramount importance than the crude measurement of adiposity through BMI[37].

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4.1. Strength and limitation of the study

This study was limited by the cross-sectional study in which a cause-effect relationship couldn't be established [38, 39]. So that longitudinal studies are needed to warrant further investigations to identify the combined impact of VCD and MetS on kidney disease. But the involvement of these clusters of disorders provides the important association between estimated dietary intake, obesity, body fat distribution, insulin action, inflammation, and endothelial, which are all important in the development of kidney disease. The strength of the study is the large sample size from a validated data set.

4.2. Theoretical and practical implication

As described in many of the scientific kinds of literature, investment in the preventive aspect of cardiometabolic syndrome is one of the smartest activities to tackle further uremic syndromes. However, investing in this demands a comprehensive package of monitoring and evaluation programs that will consider both communities involved in health education targeting lifestyle modification which enhances increased consumption of vitC containing food groups or Vitamin C fortified diets.

Hence, specific considerations tailored to metabolic syndrome, vitC, and kidney disease measured by ACR screening and monitoring mechanisms at the community level are critical to tackling further medical complications.

Despite there were vast investments of resources to improve and decrease the burden of non-communicable diseases (NCDs) such as kidney disease, there was meager evidence on how metabolic syndrome and vitamin C deficiency synergistically cause kidney disease.

5. Conclusion

The study demonstrates that vitamin C deficiency mediates the risk of developing kidney disease among patients with MetS. Being old age and African-American individuals are associated with kidney disease. So that, vitC fortified foods on prevention of kidney diseases among patients with MetS needs to be considered for patients with MetS. Moreover, there is a need to call for the concerned bodies to give special attention to African-American and old age individuals to prevent the complication of MetS into kidney disease.

Abbreviations

BMI, body mass index; CRP, C-reactive protein; DM, diabetes mellitus; MetS, metabolic syndrome; vitC, vitamin C; IR, insulin resistance; AU, albuminuria; VCD, vitC deficiency; NHANES, National Health, and Nutrition Examination Survey. BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; WC, waist circumference; FG/FBG, fasting blood glucose; TG, triacylglycerol; HDL, high-density lipoprotein; ACR, albumin creatinine ratio.

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