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ORIGINAL ARTICLE

Diabetes and cardiorenal syndrome: Understanding the "Triple Threat"

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Abstract *Objective:* Diabetes is known to be associated with chronic kidney disease (CKD) and cardiovascular disease (CVD) independently. Type 2 cardiorenal syndrome (CRS), a recently defined syndrome, is characterized by primary renal failure that progressively leads to cardiac dysfunction. The effect of diabetes on cardiorenal syndrome has not been explored in a multi-ethnic population. In this retrospective secondary analysis, the hypothesis that diabetes modifies the effect of CVD on CKD was tested.
Methods: The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey that was performed on the non-institutionalized population in the United States. All patients from the NHANES study, who were 20 years and older between the years 1999 and 2010, were included in the analysis. CKD was determined using the Cockcroft-Gault equation. The analysis was performed using a complex samples logistic regression to determine the relationship between diabetes and CRS.
Results: The prevalence of CKD among the population was 9.6% in Non-Hispanic Whites, 8.9% in African-Americans, and 4.5% in Hispanics. The overall unadjusted odds ratio for CKD to no CKD was 6.89 (95% confidence interval [CI], 6.13–7.75, $p < 0.001$). The adjusted OR was elevated, 2.25 (CI 1.56–3.23, $p < 0.001$), among individuals with diabetes but was approximately 1.0 (1.43 CI 1.16–1.76, $p < 0.05$) among patients without diabetes after controlling for medical risk factors and demographic risk factors.
Conclusion: Diabetes is strongly associated with Type 2 CRS in a nationally representative multi-ethnic population and must be considered when treating patients. Longitudinal studies should further examine this association.

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1. Introduction

Diabetes is a major cause of morbidity worldwide, simultaneously causing cardiovascular and renal dysfunction. Consequently, cardiorenal syndrome (CRS) is a complication that is closely related to diabetes and is associated with increased mortality, growing complications, and increased cost of care.[1–4] Cardiorenal syndrome can be defined as a bidirectional pathological impairment of either the heart or the kidney due to acute or chronic primary dysfunction in either organ.[5,6] Depending on the primary organ affected and the acuteness of the condition, this syndrome constitutes five subtypes.[7,8] Specifically, Type 2 CRS can be defined by chronic abnormalities in heart function, leading to kidney injury or dysfunction. Diabetes is a well-established risk factor for cardiovascular disease (CVD), and a significant proportion of diabetic patients eventually develop clinically significant nephropathy.[9–13] In the diabetic state, progressive sclerosis/fibrosis and proteinuria occur in the kidney most likely due to the overactivity of the transforming growth factor-beta system and, to some extent, the vascular endothelial growth factor system.[14] The pathogenesis of CVD in diabetes is multifactorial, involving hemodynamic forces, humoral/metabolic factors, and oxidative stress.[15–20] Additionally, it has been suggested that endothelial dysfunction may lead to the simultaneous development and progression of renal and cardiac pathology in diabetes. While the risk of microvascular complications can be reduced by intensive glycemic control in patients with type 1 and type 2 diabetes mellitus, the benefit to the cardiovascular system is less clear.[21–23] The effect of diabetes on CRS has not been explored in a nationally representative multi-ethnic population. In this retrospective secondary analysis, the hypothesis that diabetes modifies the effect of CVD on chronic kidney disease was tested.

2. Methods

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey that was performed on the non-institutionalized population in the United States by the Centers for Disease Control and Prevention and the National Center for Health Statistics.[24] All patients from the nationally representative NHANES study who were 20 years and older between the years 1999–2010 were included in the analysis. The glomerular filtration rate (GFR) was derived from the Cockcroft-Gault equation.[25,26]

Creatinine Clearance (mL/min per 1.73 m^2) = [(140 - age) x Lean Body Weight (LBW)]/Cr x 72 (For women, the value was multiplied by 0.85 to account for the smaller muscle mass compared with men).

For the purposes of this study, a GFR less than 60 mL/min per 1.73 m^2 was considered CKD as previously validated. Even though, technically, a GFR less than 90 mL/min per 1.73 m^2 is considered CKD, a high number due to an advanced age places most older people in either Stage I or Stage II CKD. CVD was determined by the self-reported diagnosis of coronary heart disease, angina, stroke, congestive heart disease, and heart attack. All respondents over the age of 20 were asked "Other than during pregnancy, have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?". For the purposes of this study, the participants who answered "borderline" or "yes" were considered diabetics. However, those participants who answered "no" were considered non-diabetics.

Hypertension was defined as an average systolic/diastolic blood pressure $\geq$140/90 mm Hg or self-reported antihypertensive medication use. The remaining participants were considered non-hypertensive. Respondents were asked about their cholesterol status. Dyslipidemia or hyperlipidemia was ascertained and determined to be present with the use of cholesterol-lowering medications, self-reported diagnosis, or a total serum cholesterol $>$ than 240 mg/dl. In diabetic subjects, this number was $>$ than 200 mg/dl and coded as 1. The remaining subjects were ascertained as not having high cholesterol. The smoking data was subdivided into a two-variable indicator as a smoker versus never smoker. The subject was considered a "smoker" if s/he reported "yes" to the question "Have you smoked at least 100 cigarettes in your entire life?" and did not answer "not at all" to the question "Do you now smoke cigarettes?" in the NHANES 1999–2010 study. Any answer by the participants, such as "don't know", "refuse", or "not sure", was recorded as missing data and was not included in the data analyses. To ascertain the race/ethnicity of the subjects, the interviewer asked "What race do you consider yourself to be?". Within the NHANES questionnaire, respondents were allowed to select one of four categories. The different categories were coded as follows: Non-Hispanic White, Non-Hispanic Black, Hispanic, and Other.

Hs-CRP was quantified using latex-enhanced nephelometry, and a high-sensitivity assay was performed using a Behring (Deerfield, IL, United States) nephelometer. The lower limit of detection of this test was 0.2 mg/L. For the continuous analyses, all values of 0.2 mg/L were coded as equal to 0.1. Studies in adults have indicated an increased risk of cardiovascular disease beginning at values $>$ 2.0 mg/L; thus, this value was used as a cut-off point for the analysis (Ridker, 2003; Ridker et al., 2005).

Before the data collection for the NHANES study, the NCHS received approval from the NCHS Research Ethics Review Board (changed from the Institute Review Board; continuance of the protocol #2011-17). The NCHS complied strictly with different laws and regulations that were written with the intent to protect the participants' confidentiality and safety (McQuillan & Porter, 2011).

2.1. Study population

All patients from the nationally representative NHANES study who were 20 years and older between the years 1999–2010 were included in the analysis.

2.2. Statistical analysis

Continuous variables were described as the mean $\pm$ standard deviation (SD). The normal distributions of the values were assessed using the Shapiro–Wilk test. The categorical variables were expressed as percentage values. The analysis was performed using a complex

samples logistic regression to determine the relationship between diabetes and Type 2 CRS. Multiple logistic regression models were used to examine the differences between diabetic and non-diabetic patients after adjusting for sociodemographic and health factors. All missing variables were excluded. All statistical analyses were performed in SAS 9.2 and SPSS 21.0.

3. Results

Data were available for 28,139 individuals (52% females vs. 48% males). Table 1 provides the data for the distribution of the demographic characteristics of the participants by the status of CKD using bivariate analysis. The prevalence of CKD in the US population within the 20–85 years old age group was 7.1% (n = 7675), which is representative of 13,797,140 individuals in the United States population. The average age of the participants with CKD was 74.4 ± 0.28 years. There was a statistically significant ($p < 0.001$) association between gender, age, race/ethnicity, and CKD. There were significantly more females (68.0%) with CKD than males as shown in Table 1. Additionally, most (73.6%) of the individuals who were 80 years or older had CKD. Among the Non-Hispanic Whites, the percentage (8.1%) with CKD was the highest.

In addition to the basic demographic descriptive statistics, the variables that may confound and modify the effect of CVD on CKD are presented in Table 1. Based on the bivariate analyses, individuals with less than a high school education had the highest percentage rates (10.4%) of CKD. Individuals with a lower socioeconomic status had higher percentage rates of CKD (9.6%) than those individuals with a higher socioeconomic status (5.7%). Finally, individuals with diabetes (14.7% vs 6.3%) and hypertension (23.3% vs. 4.3%) were more likely to have CKD than those without diabetes and hypertension.

3.1. Effect of cardiovascular disease on CKD

As shown in Fig. 1, when considering cardiovascular disease, the overall unadjusted odds ratio for CKD to no CKD was 6.89 (95% confidence interval [CI], 6.13–7.75, $p < 0.001$). As shown in Table 2 versus Table 3, the adjusted OR for CVD was elevated, 2.25 (CI 1.56–3.23, $p < 0.05$), among individuals with diabetes but approximated 1.0 (1.43 CI 1.16–1.76, $p < 0.05$) among patients without diabetes after controlling for medical (hypertension, cholesterol status, obesity, smoking status, current infection, and C-reactive protein) and demographic (education level, ethnicity, gender, and age) risk factors.

3.2. Differential effect of ethnicity and smoking

As shown in Tables 2 and 3, the adjusted OR for smoking status was elevated, 2.38 (CI 1.36–4.16, $p < 0.001$), among individuals without diabetes but approximated 1.0 (1.26 CI

Table 1 Baseline clinical characteristics of the study participants stratified by CKD status.

Variable	Total population (n = 28,139)	CKD⁻ (n = 20,464)	CKD+ (n = 7675)
Demographic Risk Factors			
Female	51.8%	50.6%	67.9%
Mean Age (SE)	47.0 (0.21)	44.8 (0.19)	74.4 (0.28)
Ethnicity			
Non-Hisp. White	80.6%	42.7%	70.5%
Non-Hisp. Black	9.3%	45.0%	10.1%
Hispanic	5.2%	5.8%	6.4%
Other	4.9%	6.5%	14.0%
Cardiovascular Disease Risk Factors			
CRP Levels (μg/ml)			
Mean CRP (SE)	0.41 (0.01)	0.41 (0.01)	0.52 (0.02)
Low (<1)	90.4%	90.5%	88.6%
Intermediate (1–2)	6.9%	6.9%	7.1%
High (>2)	2.8%	2.6%	4.4%
Diabetes	9.1%	8.3%	18.5%
Hypertension	23.7%	21.1%	56.7%
Smoking Status			
Current Smoker	23.3%	24.2%	11.5%
Former Smoker	25.3%	24.5%	36.4%
Never Smoker	51.4%	51.3%	52.1%
Obesity Status			
Normal Weight	32.4%	30.9%	52.3%
Overweight	34.3%	34.3%	33.2%
Obese	27.8%	29.0%	13.4%
Morbidly Obese	5.5%	5.8%	1.1%
Hypercholesterolemia	40.5%	39.1%	55.6%
Current Infection	2.3%	2.4%	1.4%

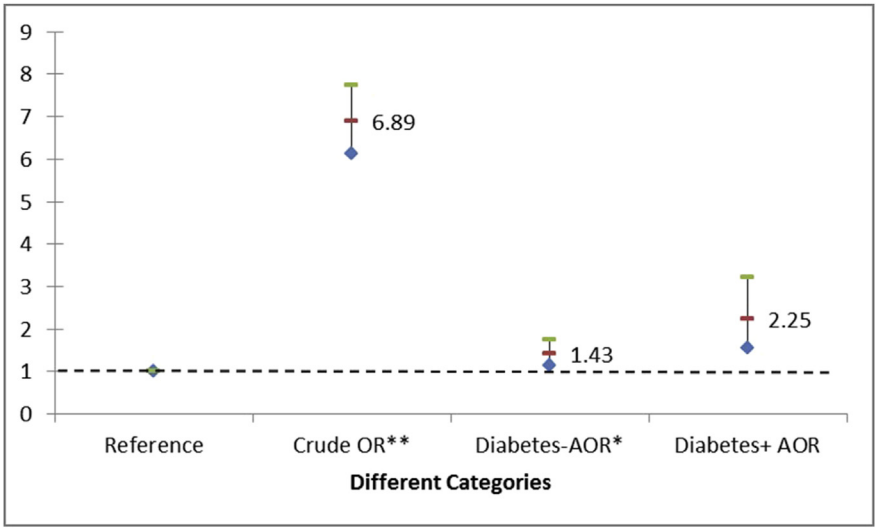

Figure 1 Crude and adjusted odds ratio of CKD in those with CVD stratified by diabetes status (**$p < 0.001$ & *$p < 0.05$).

0.87—1.84, $p > 0.05$) among patients with diabetes. Additionally, the adjusted OR for Hispanics versus non-Hispanic Whites was elevated, 1.21 (CI 0.90—1.61), among individuals with diabetes but was less than 1.0 (0.77 CI 0.48—1.23) among patients without diabetes.

4. Discussion

In this study, we found that there was a strong association between diabetes and Type 2 CRS. Individuals who have CVD and diabetes are twice as likely to develop CKD than those who do not have CVD in this nationally representative sample. Researchers have found that diabetes and cardiovascular disease independently have an impact on CKD.[27—29] Due to multi-morbidities, the risk of not reaching therapeutic targets in patients with diabetes has been shown to greater than that in people without diabetes.[29]

Additionally, other known CKD risk factors affect individuals with diabetes differently than those without diabetes. Specifically, when assessing known differences in CKD risk factors, there was a statistically significant association observed between smoking status among individuals without diabetes. However, individuals with diabetes did not demonstrate an independently statistically significant association with CKD. Diabetes is an effect modifier in the relationship between smoking and CKD. Presumably, this observation may be due to other risk factors that play a more significant role in the development of CKD among individuals with diabetes.[30—32] Similarly, ethnicity had a differential effect in the Type 2 CRS model among individuals with diabetes versus individuals without diabetes. Health care practitioners

Table 2 Multiple regression analysis of CVD and CKD in those individuals without diabetes.

Variable	β	B	95% Confidence Interval		*P*
			Lower	Upper	
Cardiovascular Disease	0.848	2.34	1.66	3.29	<0.001
Hypertension	0.521	1.69	1.09	2.61	0.020
Cholesterol Status	0.109	0.90	0.62	1.30	0.558
Obesity (Reference = BMI<30)	1.603	4.97	3.22	7.65	<0.001
Smoking Status (Reference = Never Smoker)	0.784	2.38	1.36	4.16	0.018
Current Infection	0.075	1.08	0.48	2.43	0.854
C-reactive Protein	0.157	1.17	0.47	2.90	0.552
Education Level	0.168	1.18	0.79	1.77	0.711
Sociodemographic Factors					
Ethnicity					
Non-Hisp. White	Reference	Reference	Reference	Reference	Reference
Non-Hisp. Black	−0.60	0.55	0.35	0.87	0.089
Hispanic	−0.27	0.77	0.48	1.23	0.089
Other	−0.45	0.64	0.27	1.53	0.089
Gender (Reference = Female)	0.542	1.72	1.19	2.49	<0.005
Age	0.157	1.17	1.14	1.20	<0.001

Table 3 Multiple regression analysis of CVD and CKD in those individuals with diabetes.

Variable	β	B	95% Confidence Interval		*P*
			Lower	Upper	
Cardiovascular Disease	0.446	1.59	1.27	1.98	<0.001
Hypertension	0.49	1.64	1.32	2.03	<0.001
Cholesterol Status	0.086	0.92	0.77	1.09	0.333
Obesity (Reference = BMI<30)	1.73	5.64	4.54	6.99	<0.001
Smoking Status (Reference = Never Smoker)	0.233	1.26	0.87	1.84	0.131
Current Infection	0.32	1.38	0.82	2.33	0.228
C-reactive Protein	0.39	0.68	0.40	1.16	0.367
Education Level	0.085	0.92	0.70	1.21	0.061
Sociodemographic Factors					
Ethnicity					
Non-Hisp. White	Reference	Reference	Reference	Reference	Reference
Non-Hisp. Black	−0.59	0.56	0.43	0.72	<0.001
Hispanic	0.19	1.21	0.90	1.61	<0.001
Other	−0.65	0.52	0.30	0.91	<0.001
Gender (Reference = Female)	0.829	2.29	1.79	2.93	<0.001
Age	0.176	1.20	1.17	1.21	<0.001

must be aware of how diabetes affects Type 2 CRS. According to our study, after controlling for CVD-related risk factors in a multi-ethnic population, individuals who have CVD and diabetes have a 125% higher likelihood of developing CKD than those that do not have CVD.

Consequently, diabetes may need to be addressed and monitored closely in patients with Type 2 CRS. Pharmaceutical companies are actively searching for therapeutic solutions to address this type of CRS in patients with diabetes. In a double-blind controlled trial, previous investigators from the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) trial also found that renin-inhibitors were not useful in preventing CRS.[33–35] However, diabetes may need to be addressed and monitored closely in other ways in patients with Type 2 CRS to effectively achieve therapeutic targets. Health care practitioners must be aware of this potential effect on Type 2 CRS.

There were multiple limitations in this study. First, this is cross-sectional study, making it difficult to establish causation without a reasonable doubt. More longitudinal studies must be performed to understand the precise role of diabetes in the context of CRS. Additionally, self-reported data often suffers from recall bias or social desirability bias. However, whenever possible, we cross-checked the self-reported data with laboratory tests.

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