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Early markers of kidney dysfunction and cognitive impairment among older adults

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ABSTRACT

Background: Age-related decline in kidney function can be an important risk factor for cognitive impairment in older adults. In this study, we examined several kidney function measures for the association with cognitive function in older adults in hope to identify early and sensitive markers that can be used for the detection or screening for cognitive impairment.
Methods: A total of 1982 older participants (aged ≥60 years) in the 1999–2002 National Health and Nutrition Examination Survey was analyzed for the association between kidney function and cognitive impairment using multivariate logistic regression and general linear models. Cognitive functioning was assessed during the household interview using a version of the Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale III. In our study, participants with a score of <31, the 25th percentiles of the distribution, or who were unable to complete the sample exercise due to cognitive limitations were classified as having cognitive impairment.
Results: Of 1982 older adults, 503 were having cognitive impairment (weighted prevalence, 15.38%). Among the kidney function measures that we examined, the levels of serum cystatin C and urinary albumin were found being significantly associated with cognitive impairment after adjusting for age, sex, race/ethnicity, poverty status, education, physical activity, BMI, cigarette smoking, and alcohol consumption. Cognitive functioning scores were significantly decreasing with increasing levels of kidney dysfunction markers.
Conclusion: Serum cystatin C and urinary albumin that are early markers of chronic kidney disease might serve as early and effective markers for cognitive decline in older adults. Mechanisms underlying the observed association need to be further characterized.

1. Introduction

Cognitive impairment, including Alzheimer's disease and other kinds of dementia, is a major health problem in older adults worldwide. Alzheimer's disease (AD) is the 6th leading cause of death in the United States. >5 million people are currently living with this disease, leading to an estimated 500,000 deaths each year from the complications of AD [1]. The arising cognitive decline in the aging population causes increasing burdens and costs to individuals and society. While age is the primary risk factor for cognitive impairment, other risk factors include family history, education level, brain injury, exposure to environmental chemicals, physical inactivity, and chronic conditions such as heart disease, stroke, and diabetes [2].

Chronic kidney disease (CKD) or reduced kidney function is a common health problem in the elderly [3]. Aging and CKD can affect physical function, cognition, and frailty [4]. Emerging evidence from population-based studies suggests an association between reduced kidney function and cognitive impairment in older adults [5–17]. Studies have shown that older study participants with lower estimated glomerular filtration rate (eGFR) had lower cognitive performance [6,7,9,11,14–16]. Moderate renal impairment, defined by a higher level of serum creatinine, was found to be associated with an excess risk of incident dementia among individuals in good-excellent health in a cohort study [5]. Higher serum cystatin C levels, an early and reliable marker of kidney function, were also reported being associated with worse cognition and greater likelihood of poor cognitive performance on attention, executive function, and naming [13]. In addition, increased protein excretion, measured as urine protein/creatinine ratio, was shown to be associated with cognitive dysfunction in patients with Lewy body disorders [17].

Although a number of studies have linked kidney dysfunction to increased risk of cognitive impairment, there have been some inconsistency about the findings, particularly on which renal function markers exhibiting significant associations with cognition. The objectives of the current study were to further evaluate the relationship between kidney

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function and cognitive impairment and to identify renal function markers that are significantly associated with impaired cognition and can be used as markers for cognitive decline in older adults. To achieve this, we examined the association between kidney function measures and cognitive impairment in older adults, aged 60 years or older, who participated in the 1999–2002 U.S. National Health and Nutrition Examination Survey (NHANES). The prevalence of cognitive impairment was determined in the representative sample of the US older population as well as by different demographic and behavioral groups. Several kidney function measures that are available from the NHANES, including serum levels of creatinine, cystatin C, BUN, uric acid, and urinary albumin, were analyzed for the association with cognition. Concentrations of kidney function measures were determined for the groups with varying cognitive function.

2. Methods

2.1. Study participants

The NHANES is an ongoing cross-sectional survey of a nationally representative sample of the noninstitutionalized U.S. civilian population conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention [18]. The survey has been conducted continuously and released in 2-year cycles since 1999. To obtain survey estimates with greater precision, we combined the two data collection cycles of 1999–2000 and 2001–2002 for the present study. To obtain a nationally representative sample, the NHANES study participants are selected from counties across the country using a complex multistage stratified probability sampling design. Participants aged 60 years or older were included for the purpose of our study. All procedures were approved by the NCHS Research Ethics Review Board and all participants provided written informed consent. Participants were interviewed and followed by a detailed physical examination and collection of urine and blood samples in a mobile examination center by trained health technicians.

2.2. Kidney function measures

Data on kidney function measures, including serum creatinine, urinary albumin, serum cystatin C, blood urea nitrogen (BUN), and serum uric acid, were extracted from the dataset. Serum creatinine, BUN, serum uric acid measurements were performed on a Hitachi Model 704 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). The Jaffe kinetic alkaline picrate method was used to measure concentrations of serum creatinine in the NHANES. To correct for measurement differences from the standard method, serum creatinine was standardized by the formula of $1.013 \times$ NHANES Creatinine $+ 0.147$, as recommended by the NHANES. The cystatin C measurements were conducted using the Dade Behring N Latex Cystatin C assay which is an automated particle-enhanced nephelometric assay. Urinary albumin was determined using a solid-phase fluorescent immunoassay. Detailed methods for these measurements are described in the NHANES Laboratory Procedures Manuals [19].

2.3. Cognition assessment

Cognitive functioning in the NHANES study participants 60 years of age or older was assessed during the household interview using a version of the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III [20]. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133. Detailed procedures of how to measure cognitive functioning are described elsewhere [21]. The DSST measures several interrelated cognitive domains for its completion, including response speed, sustained attention, visual spatial skills, associative learning, and memory.

For our data analyses, we classified study participants using a cognitive functioning score of 31, the 25th percentile of the distribution, as the cutoff value. Participants with a score of <31 or who were unable to complete the sample exercise due to cognitive limitations were classified as having cognitive impairment. Participants with a score of ≥ 31 were classified as not having cognitive impairment. We also used the test score as continuous variable in the analyses.

2.4. Covariates

We considered the age, sex, race/ethnicity, poverty status, education, BMI, physical activity, cigarette smoking, and alcohol consumption as potential confounders in our analysis. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican American and other Hispanic), and other (Asian and other, including multi-racial). Poverty status was classified as family income to poverty ratio <1 versus ≥ 1. Education was categorized as less than high school and high school graduate or higher. Physical activity was categorized as self-reported moderate or vigorous physical recreational activity versus none. For cigarette smoking, participants were classified as never, current, or past smokers, based on the questionnaire data. Alcohol consumption was classified into “yes” or “no” based on the question “In any one year, have you had at least 12 alcohol drinks?”.

2.5. Statistical analysis

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). Since the population was selected using a complex probability sample procedure, sample weights were incorporated into the analysis to get proper estimates and confidence intervals of estimates, according to the NHANES guidelines [22]. Descriptive statistics was performed on weighted characteristics of the study population by cognitive performance. Concentrations of kidney function measures were determined for the total study population and for the cognitive functioning groups. Multivariate logistic regression analyses were performed to assess the association between kidney function measures and cognitive impairment. A multivariate general linear model was also constructed to examine changes in cognitive functioning scores in association with concentrations of kidney function measures. Considering the highly skewed distribution of serum levels of creatinine, cystatin C, BUN, and urinary albumin, we log-transformed these values when conducting the analyses. Both unadjusted and adjusted models were constructed. Results were considered statistically significant at α level of 0.05 and all statistical tests were two-sided.

3. Results

During the study period of 1999–2002, a total of 3706 study participants were 60 years or older, and being assessed for cognitive functioning. We excluded participants who were unable to complete the exercise and had no scores ($n = 731$), from which, however, 69 participants who were unable to complete the sample exercise due to cognitive limitations were kept in the analyses; therefore, the sample size was reduced to 3044. We further excluded participants with missing any values of kidney function measures included in our study ($n = 538$) and with missing covariates included in our models ($n = 524$). The final sample size was 1982 in the analyses.

3.1. General characteristics of the study participants

Of 1982 older adults, 503 were having cognitive impairment (weighted prevalence, 15.38%). Table 1 shows weighted characteristics of the study participants with and without cognitive impairment. The