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Understanding the direction of the relationship between white matter hyperintensities of vascular origin, sleep quality, and chronic kidney disease—Results from the Atahualpa Project

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A R T I C L E I N F O

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A B S T R A C T

Objective: The burden of cerebral small vessel disease, sleep disorders, and chronic kidney disease is on the rise in remote rural settings. However, information on potential links between these conditions is limited. We aimed to assess the relationships between these conditions in community-dwelling older adults living in rural Ecuador.
Patients and Methods: Atahualpa residents aged ≥60 years were offered a brain MRI. A venous blood sample was obtained for serum creatinine determination. Baseline interviews and procedures were directed to assess demographics, cardiovascular risk factors, and sleep quality. Using generalized structural equation modeling (GSEM), we assessed the associations between white matter hyperintensities (WMH) of vascular origin, sleep quality and kidney function, as well as the directions of the relationships between these variables.
Results: Of 423 candidates, 314 (74%) were enrolled. Moderate-to-severe WMH were noticed in 74 (24%) individuals, poor sleep quality in 101 (31%), and moderate-to-severe chronic kidney disease in 28 (9%). GSEM showed that the direction of the effect was from kidney function to WMH and from the latter to sleep quality. Of independent variables investigated, worse kidney function was associated with age, high glucose levels and male sex. WMH was associated with cholesterol blood levels, blood pressure, level of education and severe edentulism. Poor sleep quality was associated with poor physical activity.
Conclusion: This population based study shows that chronic kidney disease is associated with increased severity of WMH, which, in turn, is associated with a poor sleep quality.

1. Introduction

Prevalence of stroke, sleep disorders and chronic kidney disease are on the rise in most of the developing world [1–3]. While it is possible that the increased burden of these three major public health problems have occurred independently, it is conceivable that some kind of relationship does exist between these conditions, explaining this simultaneous increase over the past few decades. In this view, there is growing evidence favoring an association between white matter hyperintensities (WMH) of presumed vascular origin – a major neuroimaging signature of cerebral small vessel disease – and chronic kidney disease [4–9]. There is additional evidence suggesting an association between WMH and sleep-related symptoms [10–14]. To add complexity to the aforementioned interactions, recent studies have shown an association between abnormal sleep and chronic kidney disease [15,16] probably increasing the risk of cerebrovascular events.

In the present study, generalized structural equation modeling (GSEM) was used to better evaluate and understand the relationship between WMH, sleep quality, and chronic kidney disease in the setting of the Atahualpa Project, an ongoing population-based cohort study designed to reduce the burden of non-communicable diseases in rural Ecuador [17]. GSEM is a comprehensive, flexible approach to model complex interrelationships amongst a number of variables where some may be considered cause and some effect.

2. Patients and methods

2.1. Study population

Atahualpa is a rural village located in coastal Ecuador. As detailed elsewhere, residents are homogeneous regarding race (95% belong to the native/mestizo ethnic group), living conditions, socio-economic status, and dietary habits [17]. Shift working is virtually inexistent among villagers and light pollution during night hours is limited.

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Atahualpa is a closed village with a low migration rate (less than 30 adults leave the village every year), which make this an optimal setting for conducting population-based studies [18].

2.2. Study design

The subset of Atahualpa residents aged ≥60 years identified during door-to-door surveys and prospectively enrolled in the Atahualpa Project (n = 423) were offered a brain MRI, and those who signed the informed consent and had no contraindications for the practice of this exam were registered in the Neuroimaging Substudy (n = 351). Baseline interviews and procedures were directed to assess demographics, cardiovascular risk factors, and sleep quality (see below). Thereafter, all individuals who had a brain MRI were invited to participate in the present study, and a venous blood sample for serum creatinine determination was drawn in 319 (91%) consenting subjects. Blood samples were drawn and centrifuged at the Community Center of the Atahualpa Project, and transported on ice to the laboratory (International Laboratory Services, S.A., Guayaquil) for further processing and analyses. The study was approved by the Institutional Review Board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867).

2.3. Neuroimaging protocol

MRIs were performed with a Philips Intera 1.5T (Philips Medical Systems, Eindhoven, the Netherlands) at Hospital-Clínica Kennedy, following a standardized protocol described elsewhere, which included two-dimensional multi-slice turbo spin echo T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a FLAIR sequence oriented in the sagittal plane [19]. Interest focused on the presence of white matter hyperintensities (WMH) of presumed vascular origin, defined as lesions appearing hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation) and graded according to the modified Fazekas scale in none, mild, moderate and severe [20]. Two experienced readers, blinded to clinical data, independently reviewed all MRIs. Kappa coefficient for inter-rater agreement was 0.91 (95% C.I.: 0.86–0.95), and discrepancies were resolved by consensus.

2.4. Sleep quality assessment

Trained medical students assessed sleep quality by the use of a validated Spanish version of the Pittsburgh Sleep Quality Index (PSQI), as previously described [21]. The PSQI basically discriminates between "good" and "poor" sleepers. Time-frame of such evaluation is in the month before the test. It consists of 19 items grouped into seven components, each weighted on a 0–3 scale, for a total score of 21 points, with a score of ≥6 indicating a poor sleep quality. Components include assessment of sleep duration (total sleep time), sleep disturbances, sleep latency, daytime dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and medications needed to sleep.

2.5. Categorization of kidney function

Kidney function was evaluated by the estimated glomerular filtration rate (eGFR), obtained by the use of the abbreviated Modification of Diet in Renal Disease study equation, which relies on serum creatinine, age, sex, and ethnicity of the individual (eGFR = 186 x serum creatinine $[\mathrm{mg/dL}]^{-1.154}$ x $\mathrm{age}^{-0.203}$ x 0.742 if women x 1.212 if African American) [22]. Since we did not have African American people in our study population, we did not use the 1.212 constant in any case. The eGRF was trichotomized according to kidney function: > 90 mL/min (normal function), 60–90 mL/min (mild chronic kidney disease), and 15-59 mL/min (moderate-to-severe chronic kidney disease). Patients with end-stage kidney failure (eGRF < 15 mL/min) were excluded from analyses.

2.6. Covariates investigated

Demographics and cardiovascular risk factors were selected as confounding variables, and assessed through interviews and procedures previously described in the Atahualpa Project [23]. In brief, we used the seven health metrics (and cutoffs) proposed by the American Heart Association to assess the cardiovascular health status, including: smoking status, physical activity, diet, the body mass index, blood pressure, fasting glucose, and total cholesterol blood levels [24]. In addition, severe edentulism (less than 10 remaining teeth) was used as a surrogate of chronic inflammatory periodontal disease, and was included as a covariate as it has shown to be related to neuroimaging signatures of SVD in older adults living in Atahualpa [25].

2.7. Statistical analysis

Data analyses are carried out by using STATA version 14 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or Fisher exact test as appropriate. The independent association between kidney function and WMH, as well as that between kidney function and sleep quality were assessed by the use of logistic regression models adjusted for demographics and cardiovascular risk factors. A multinomial logistic regression analysis was used to investigate the independent association between WMH and sleep quality, after adjusting for the same confounders.

GSEM analyses were conducted in two steps. Our approach was a "hypothesis driven analysis". Therefore, the best fitted model was not chosen by fitting all possible models. Instead, the selection of measured (observed) and latent (unobserved) variables was directed by our prior publications on the matter, and were examined for co-linearity, and each of the three dependent variable (kidney function, WMH and sleep quality) were independently tested for the multivariate association with all covariates (demographics and cardiovascular risk factors) using an appropriate linear model (Gaussian or Logistic). Next, the potential risk factors (measured, observed variables) were incorporated into a GSEM model with successive iterations improving the model goodness of fit (AIC and BIC) until the best fitting model was obtained. All models were hypothesis driven. A latent variable (Risk) was hypothesized to affect primarily WMH, but was also tested against the other dependent variables. GSEM was then utilized to better understand the complex interrelationships between kidney function, WMH and sleep quality. The hypothesis that we modeled and evaluated was that there were independent risk factors, which affect all three dependent variables and that there may be a potentially causal association between them. Furthermore, we hypothesized the direction of the relationship between the main dependent variables. The direction from and to the main dependent variables were set according to the literature and our previous observations in the Atahualpa Project. That is, abnormal kidney function is associated with increased severity of WMH, and WMH has a deleterious effect on sleep quality. This was always the start of the model.

3. Results

Five of 319 eligible individuals were excluded due to end-stage kidney disease (eGFR < 15 mL/min). Table 1 shows the characteristics of participants and across categories of WMH, sleep quality and kidney function. In univariate analyses, moderate-to-severe WMH were significantly associated with increasing age ($p < 0.001$), primary school education ($p < 0.001$), poor physical activity ($p < 0.001$), poor diet ($p = 0.017$), blood pressure ≥ 140/90 mmHg ($p = 0.006$), poor sleep quality ($p = 0.004$), the PSQI score ($p = 0.001$), the eGFR in mL/min ($p = 0.001$) and marginally associated with any grade of chronic