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Diabetic nephropathy is an independent factor associated to severe subclinical atheromatous disease

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ABSTRACT

Background: Atheromatous disease (AD) is a risk factor for death in renal patients. Traditional CV risk factors do not predict the presence of AD in this population. The aim of this study is to analyze whether the etiology of the primary renal disease influences in the risk of having silent AD.
Study design: Observational cross-sectional study in chronic kidney disease patients without previous cardiovascular events.
Settings and Participants: 2436 CKD subjects without any previous CV event included in the prospective Spanish multicenter NEFRONA study. Patients were classified according to primary renal disease: diabetic nephropathy (n = 347), vascular nephropathy (n = 476), systemic/glomerular disease (n = 447), tubulointerstitial and drug toxicity nephropathy (n = 320), polycystic kidney disease (n = 238), non-filiated nephropathy (n = 406) and other causes (n = 202).
Predictors: B-mode and Doppler ultrasonography analysis of the carotid arteries were performed to measure intima media thickness (IMT) and the presence of plaques. Clinical and laboratory parameters related to CV risk were also determined.
Outcomes: AD was scored according with the ultrasonography findings and the ankle-brachial index into two large groups: absence or incipient AD and severe AD.
Results: In multivariate regression analysis, older age (OR 1.09/year [1.088–1.108]), smoking habit (OR 2.10 [1.61–2.74]), male gender (OR 1.33 [1.09–1.64]), grade-5D of CKD (OR 2.19 [1.74–2.74]), and diabetic nephropathy (OR 2.59 [1.93–3.48]) are independent risk factors for severe AD. The prevalence of silent AD was highest for diabetic nephropathy with grade-5D of CKD (82.2%) and lowest with stages 2–3 CKD systemic/glomerular disease (36.6%).
Limitations: Observational study with the potential for confounding.
Conclusion: In CKD patients without any CV event in the background clinical history, diabetic nephropathy as primary renal disease is the most significant factor associated to severe silent AD. Furthermore, this difference was independent of other conventional risk factors for atherosclerosis and CV events.

1. Introduction

Cardiovascular (CV) events represent the leading cause of mortality for patients with renal disease as well as for the general

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population [1]. Furthermore, chronic kidney disease (CKD) is a well-known risk factor for CV disease. CV mortality in end-stage renal disease (ESRD) patients is around 10–15 times higher than in the general population [2,3]. The high CV mortality in CKD patients highlights the lack of efficacy of the prophylactic strategies taken to date. For instance, different studies fail to show a beneficial effect of using statins or ACE inhibitors in reducing CV risk in ESRD patients [4–6]. Traditional CV risk factors underestimate the atheromatous disease in this population [7]. In this regard, efforts should be addressed to detect patients at *higher risk*. Since carotid atheromatous disease (AD) is related to coronary disease and CV risk [7,8] the use of imaging techniques such as carotid ultrasound may add valuable information in the study of the population with renal disease. Thus, we have previously shown in the NEFRONA Study that the presence of carotid plaques is significantly increased even in early stages of renal disease [9,10] Furthermore, the information provided by the analysis of arterial stiffness in addition to imaging techniques improves overall knowledge of the AD of the patients [11,12].

Recent guidelines recommend classifying CKD based on etiology, estimated glomerular filtrate (eGFR) and urinary albumin/creatinine ratio [13]. Previous observational studies have been limited to assess the relevance of the etiology of kidney disease to the kidney disease progression [14,15]. Recently, a subanalysis of the Study of Heart and Renal Protection (SHARP) has suggested that the causes of CKD have substantial prognosis implications in the risk of ESRD. Thus, patients with cystic kidney disease are at much higher risk of ESRD and much lower risk of death. By contrast patients with diabetic nephropathy (DN) are at high risk of death before reaching ESRD [15]. These findings point out that etiology of renal disease influences the prognosis of renal outcome but differ in the prognosis of death.

In the present study we hypothesized that the type of underlying kidney disease in CKD patients may be associated with a different risk of subclinical AD, and could help us to better detect and stratify CV risk in the CKD population. Notably, the relationship between the etiologies of the renal disease and CV risk, especially in patients with subclinical AD, has been scarcely analyzed. Our aim is to study whether the etiology of the renal disease affects the risk of having silent AD in a large population with different stages of CKD and complete absence of any CV event in their background.

2. Methods

2.1. The NEFRONA study

Study samples were obtained from the NEFRONA study. This is a multicenter, prospective observational study aimed to assess the predictive value of imaging techniques and biomarkers for CV disease in a large group of patients from outpatient clinics in nephrology departments with different grades of CKD and renal-healthy subjects, as previously described [16,17]. Briefly, 3004 subjects aged 18–75 years old were enrolled from 81 Spanish centers between October 2010 and June 2012. The exclusion criteria were: previous CV events, active infections (HIV, tuberculosis), pregnancy, having received any organ transplantation or having a life expectancy of less than 1 year. Each physician team recorded etiologies of kidney disease according to the evidences of patient's clinical history. The eGFR was calculated using the Modification of Diet in Renal Disease Study (MDRD4) equation. Each local ethics committee approved the study, and subjects were included after providing informed consent. Subjects were stratified according with the KDIGO-CKD guidelines in different grades of CKD. For our analysis we only included patients with eGFR <60 ml/min/1.73 m^2 or between 60 and 89 ml/min/1.73 m^2 if they had a urine albumin to creatinine ratio higher than 300 mg/g (Grade2 A3). Subjects were subsequently categorized into 7 groups according to the etiologies of CKD: diabetic nephropathy (DN), vascular nephropathy (VN), glomerular and systemic disease (Systemic/Glom), tubulointerstitial and drug toxicity nephropathy (TIN), polycystic kidney disease (Cystic), non-filiated nephropathy and other causes ("Others") in which we include genetic, tumor, renal hypoplasia among others.

2.2. Clinical and biochemical data

At recruitment, patients were asked to complete a questionnaire including family history on premature CV disease, clinical history (diabetes mellitus, hypertension and dyslipidemia), CV risk factors (such as smoking habit), and medication use. Biochemical parameters were obtained from a routine blood test performed within a 3-month period of the vascular exploration. Blood pressure was measured with a validated semi-automatic oscillometer (Omron HEM-705CP).

All subjects underwent ultrasound exploration to evaluate the carotid and femoral arteries. For this study we analyzed data obtained from carotid exploration. The ultrasound was performed according to a standardized protocol by three itinerant teams uniformly trained (a nurse and a radiology technician) belonging to the UDETMA (Unit for Detection and Treatment of Atherothrombotic Diseases, Hospital Universitari Arnau de Vilanova, Lleida, Spain). The itinerant teams also collected the anthropometric parameters as well as blood samples, which were stored within 24 h at the centralized biobank of the Spanish Network for Nephrological Research (REDinRen) at the University of Alcalá (Madrid, Spain).

2.3. Carotid ultrasound

Analysis of the carotid arteries were performed to measure intima media thickness (IMT) and the presence of plaques. B-mode ultrasound of the carotid arteries was performed using the Vivid BT09 apparatus (General Electric instrument) equipped with a 6–13 MHz broadband linear array probe. A unique reader in a blinded fashion performed the analysis by using the semi-automatic software EchoPAC Dimension (General Electric Healthcare). To assess the quality of the reading and the intra-observer reliability, a sample of 20 individuals was measured 3–5 times on different days. A kappa coefficient of 1 was obtained, indicating excellent intra-observer reliability.

2.4. Ankle-brachial index

Vascular Doppler MD2 Hungleigth was used with an 8 MHz transducer and a sleeve for making manual blood pressure. The determination of blood pressure was performed in the brachial artery in both arms and in both feet. To calculate the ankle-brachial index (ABI) the higher brachial blood pressure was used or the closest in time to the malleolar measure.

2.5. Severity of atheromatous disease

Atheromatous disease (AD) was initially scored in 4 groups according with the ultrasonography findings and the ABI measurement [18,19]: Stage 0; subjects with ABI > 0.9 and IMT < 80% according reference range (RR). Stage 1; ABI between 0.7 and 0.9 and/or carotid IMT $\geq$ 80% according (RR): Stage 2; carotid plaque without stenosis (peak systolic velocity < 125 cm/s), Stage 3; ABI < 0.7 and/or carotid plaque with stenosis >50% (peak systolic velocity $\geq$ 125 cm/s). Finally, we separated our population into two large groups: Absent/incipient AD (Stage 0–1) and severe AD (Stage