Cardiovascular risk factors underestimate atherosclerotic burden in chronic kidney disease: usefulness of non-invasive tests in cardiovascular assessment

Blai Coll1, Àngels Betriu1, Montserrat Martínez-Alonso2, Mercè Borràs1, Lourdes Craver1, Maria Luisa Amoedo3, MPaz Marco1, Felipe Sarró1, Mireia Junyent1, Jose Manuel Valdivielso1,* and Elvira Fernández1,*

1Unitat de Diagnòstic i Tractament de Malalties Aterotrombòtiques (UDETMA), Nephrology Department, 2Institut de Recerca Biomèdica de Lleida, Hospital Universitari Arnau de Vilanova, Lleida, Spain and 3Hospital de Torrevieja, Alicante, Spain

Correspondence and offprint requests to: Blai Coll; E-mail: bcoll@arnau.scs.es

*J.M.V. and E.F. share senior authorship

Abstract

Background. Cardiovascular risk scoring (Score) does not specifically address chronic kidney disease (CKD) patients. The aim of our study is to quantify atherosclerosis using carotid ultrasound and ankle–brachial index (ABI) and to assess its additional value in risk scoring.

Methods. In this cross-sectional, observational study, patients were studied according to a standardized protocol including carotid ultrasound and ABI to determine the atherosclerosis score (AS), ranging from absence of to severe atherosclerosis (AS 0 to AS 3).

Results. We included 409 CKD-affected patients (231 on dialysis, 99 in CKD Stages IV–V and 79 in CKD Stages I–III) and 851 subjects with normal renal function. The presence and severity of atherosclerosis was significantly higher in the CKD group than in the controls at every decade of age studied. Among the CKD-affected subjects, the prevalence of carotid plaques was significantly higher in the dialysis group (78.3%) than in the group in CKD Stages I–III (55.6%, P < 0.001). We identified 174 patients at low–intermediate risk. Among them, 110 (63.2%) presented either moderate (AS 2) or severe (AS 3) atherosclerosis. Variables significantly (P < 0.05) and positively related to atherosclerosis being on dialysis [OR = 3.40, 95% CI (1.73–6.78)] vs CKD Stages I–III, age [OR = 1.08, 95% CI (1.06–1.11)] and C-reactive protein [OR = 1.04, 95% CI (1.01–1.08)]. Conversely, female sex was negatively related to atherosclerosis [OR = 0.40, 95% CI (0.23–0.71), P = 0.002].

Conclusion. The use of carotid ultrasound and ABI identifies atherosclerosis in a population of CKD patients in which risk scoring underestimates atherosclerosis burden.

Keywords: ankle–brachial index; atherosclerosis; carotid ultrasound; chronic kidney disease

Introduction

The most prominent cause of mortality among chronic kidney disease (CKD)-affected patients is cardiovascular events [1] and, therefore, cardiovascular disease (CVD) prevention is of paramount relevance. However, most of the existing data on cardiovascular risk scores (Framingham score) come from the general population and might not be equally applied to CKD patients [2]. In a study of 936 patients on haemodialysis, neither serum total cholesterol nor systolic blood pressure was associated with coronary heart disease, cerebrovascular disease or peripheral vascular disease, and the authors concluded that using the Framingham score in haemodialysis patients is inadequate in predicting coronary heart disease [3]. Furthermore, variables involved in the pathogenesis of atherosclerosis of...
CKD, such as anaemia [4], chronic inflammation/oxidative stress [5] or mineral metabolism-related disturbances [6,7], are not reflected in CVD risk scoring. In this scenario, the National Kidney Foundation's (NKF) Kidney Disease: Improving Global Outcomes initiative supports the use of non-invasive tests (e.g., ultrasound of the carotid arteries) for a better cardiovascular assessment [8]. However, data comparing traditional CVD risk factors with the study of atherosclerosis burden in CKD patients is scarce and, consequently, practice guidelines are not precise enough to adequately counsel when and in whom these techniques should be applied.

The aim of our study is to quantify atherosclerosis burden of CKD patients using an early atherosclerosis detection model, based on carotid ultrasound and ankle–brachial index (ABI), and to analyse additional information along with traditional risk scoring.

Materials and methods

Design

This is a cross-sectional, observational study performed in four different dialysis centres in Spain. The core centre of the study, along with the nephrology outpatient clinic, is based in a university-based hospital (Hospital Universitari Arnau de Vilanova). The protocol has been reviewed and approved by the ethical review board of the hospital, and each participant signed an informed consent document before being included into the study. Inclusion period was set at 6 months, during which we consecutively invited patients to participate.

Study population

We included both modalities of dialysis, haemodialysis (N = 207) and peritoneal dialysis (N = 24). We did not exclude participants according to age, previous CVD or concomitant medical conditions, with the aim of having a representative population of chronic kidney disease Stage V on dialysis (CKD-V/D) patients.

We similarly recruited patients at earlier stages of CKD, I–IV and V (no dialysis) from the specialized nephrology outpatient clinic.

We have also included data of 851 subjects with normal renal function which were used as a control population. Participants were recruited in the primary care setting and participated in a primary prevention cardiovascular trial [9]. Briefly, male and female subjects, aged 40–74 years and without previous CVD, with at least one of the following criteria were eligible for the study: Score at low to intermediate CVD risk; early appearance of major cardiovascular events in the family (age: males <55 years or females <65 years); Type 2 diabetes mellitus or total cholesterol ≥320 mg/dl (mmol/L) or LDL cholesterol ≥240 mg/dl (mmol/L).

Procedures and variables

Clinical and laboratory data were used to calculate Score (Score: low CVD risk) [10]. Highly specialized and trained personnel, blinded to any of the clinical and laboratory information of the participants, performed the following procedures:

1. Measurement of ABI: we used a vascular Doppler MD2 Huggleight with an 8-MHz transducer. Brachial systolic pressures were obtained in both arms and ankle systolic pressures were measured. We used maximum brachial systolic pressures and recorded ABI as the lowest value obtained in each region.
2. Carotid ultrasound: we performed the carotid ultrasound to measure carotid intima–media thickness (cIMT) and to identify the presence of carotid plaques. We used a MicroMaxx SonoSite with a linear transducer HFL38/13–6 MHz.

Each examination was performed using the same standard operational procedure, which is as follows:

- Trans loop: a cross-sectional loop of the region of interest (common carotid artery, bulb and internal carotid artery) was evaluated to identify atheroma plaques.
- Longitudinal images: as it is defined in the consensus [11], we analysed the last centimetre of the far wall of the common carotid artery, the bulb section and, finally, the first centimetre of the internal carotid artery. The measurement of the cIMT was performed using the semi-automated, Food and Drug Administration (FDA)-approved software, SonoCalc IMT®.
- Pulsed Doppler: we used the colour and pulsed Doppler once an atheromatous plaque was identified (significant stenosis is considered when a systolic velocity peak >125 cm/s is reached).

Definitions

CKD was defined as recommended by current guidelines [12]. CVD was considered when ischaemic coronary heart disease, stroke or peripheral arterial diseases were present.

Fig. 1. Atherosclerosis Score (AS) definition. ABI, ankle–brachial index; cIMT, carotid intima–media thickness; RI, reference interval.
We set an atherosclerosis score (AS) (Figure 1) based on the results of non-invasive tests:

1. No atherosclerosis (AS 0): ABI >0.9 and cIMT inferior to the cut-off value representing the 80% reference interval (RI), adjusted by age and sex. RI values have been obtained from previously published observational studies using the same ultrasound procedures [13, 14].

2. Mild atherosclerosis (AS 1): an ABI 0.7–0.9 and/or cIMT superior to the cut-off value of the 80% RI.

3. Moderate atherosclerosis (AS 2): the presence of a carotid plaque without significant stenosis (<125 cm/s) and ABI ≥0.7.

4. Severe atherosclerosis (AS 3): an ABI <0.7 and/or the presence of a carotid plaque with significant stenosis (>125 cm/s).

Statistical analyses

Univariate descriptive statistics were performed and differences among CKD types (I–III, IV–V with and without dialysis) were tested using the analysis of variance test for comparisons between means of numerical skewed variables and the Pearson chi-square test to compare frequency distributions of categorical variables (substituted by Fisher's exact test when needed). We applied post hoc analyses (Bonferroni tests) for multiple paired comparisons among CKD types. Since there were just 24 patients on peritoneal dialysis, both groups of patients receiving replacement therapies (haemodialysis and peritoneal dialysis) were grouped together. The AS classification (from AS 0 to AS 3) is used to study atherosclerosis burden and its related variables, once recoded into two groups to extract those with moderate or severe atherosclerosis (AS 2 and AS 3). In order to identify the socio-demographical and clinical characteristics that predict moderate or severe atherosclerosis, a multivariate logistic regression model was estimated, keeping in the model only those characteristics with a statistically significant relationship (P-value <0.05) or a confounding effect over any of the coefficients of the rest of the variables, defined as a change of more than 20% in any of the other coefficients once the potentially confounding variable is included in the model.

Results

Atherosclerosis assessment in CKD and control groups

We included 409 patients (231 on dialysis, 99 in Stages IV–V and 79 in Stages I–III of CKD) and 851 controls. Selected characteristics according to different decades of age are listed in Table 1. Control subjects were predominantly male but there were no differences in the prevalence of diabetes mellitus. Conversely, among the groups of CKD patients, the prevalence of hypertension was significantly higher, with the exception of those in the group ≥71 years. Total cholesterol and LDL cholesterol values (data not shown in the table) were significantly higher in the control group in every age group than in the CKD groups, as it was with the mean Score values. Nevertheless, the presence and severity of atherosclerosis (measured by the AS) was significantly higher in the CKD group (P < 0.001 in every age group).

General characteristics of CKD-affected population and atherosclerosis assessment

Patients in CKD Stages IV–V were significantly older (mean age, 70.5 years) than those on dialysis (64.8 years) or in CKD Stages I–III (61.8 years), both paired comparisons with a P-value <0.001. The prevalence of CVD was significantly higher in those patients on dialysis (40.7 vs 21.2 and 13.9%, respectively, P < 0.001). Body mass index, total cholesterol, HDL cholesterol and LDL cholesterol were significantly lower in the group of patients on dialysis in comparison with the other groups (P < 0.001). Conversely, C-reactive protein and ferritin levels were significantly higher while albumin concentration was significantly lower in the dialysis group (P < 0.001). In this group, patients were on dialysis for a median of 30.44 months (observed inter-quartile range [18.10, 70.45]) (Table 2).

We found a significantly (P < 0.001) higher presence of carotid plaques in the dialysis group [181 (78.3%)] in comparison with those in CKD Stages I–III [44 (55.6%)] and controls [367 (43.2%)]. For the Stages IV–V CKD group [70 (70.7%)], there were no significant differences (adjusted by Bonferroni). Similarly, the group on dialysis presented a significantly higher percentage of participants in AS 2 and AS 3 [193 (83.6%)] than Stages I–III CKD patients [46 (58.2%)] and controls [381 (44.9%)], whereas the percentage of these diagnoses in Types IV–V CKD [73 (73.7%)] was not statistically different from any of the other groups (adjusted by Bonferroni). It is interesting to remark that 77 (33.3%) patients on dialysis presented an AS 3, indicating very severe atherosclerosis. The presence of AS 3 was significantly lower in CKD Stages IV–V [24 (24.2%)], CKD Stages I–III [12 (15.2%)] and controls [14 (1.6%)].

We further analysed subjects according to the results of the ABI as previously reported [15]. The majority of subjects presented ABI results in the normal range (0.91–1.40); 85.6% of controls, 69.6% in the CKD Stages I–III group, 54.5% in the CKD Stages IV–V group and 46.8% in the dialysis group), and just 36 patients on dialysis (15.6%) presented an ABI ≥1.41, indicating the presence of incompressible arteries.

Clinical and laboratory values of participants according to AS and CKD stage are displayed in Table 3. Patients without atherosclerosis (AS 0/1) were significantly younger and without previous CVD at any stage of CKD. Overall, we did not find significant differences in serum albumin, calcium, phosphorus and PTH among groups (with or without atherosclerosis at different stages of CKD).

LDL cholesterol in patients with moderate/severe atherosclerosis

We analysed participants with moderate/severe atherosclerosis (AS 2 or AS 3, N = 691), depending on the levels of LDL cholesterol (Figure 2). The majority of patients presented LDL cholesterol concentrations below 100 [144 (75.4%) on dialysis, 54 (75.0%) with Types IV–V CKD]. Conversely, we just found 27 (58.7%) patients with atherosclerosis (AS 2/3) and Types I–III CKD with LDL below 100 mg/dl (P = 0.084). This percentage was further reduced when controls were analysed, since just 21.2% presented an LDL concentration below 100 mg/dl (P < 0.001). Overall, we found 85 patients at different stages of CKD with AS 2/3 and LDL cholesterol concentration above 100 mg/dl (Figure 2).
### Table 1. General characteristics of the study population

<table>
<thead>
<tr>
<th>Age, years</th>
<th>≤50 years</th>
<th>51–60 years</th>
<th>61–70 years</th>
<th>≥71 years</th>
<th>P-value</th>
<th>Control (N = 239)</th>
<th>CKD (N = 60)</th>
<th>Control (N = 315)</th>
<th>CKD (N = 56)</th>
<th>Control (N = 244)</th>
<th>CKD (N = 109)</th>
<th>Control (N = 53)</th>
<th>CKD (N = 183)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (%)</td>
<td>161 (67)</td>
<td>22 (36)</td>
<td>185 (58)</td>
<td>7 (12)</td>
<td>&lt;0.001</td>
<td>146 (57)</td>
<td>17 (28)</td>
<td>164 (52)</td>
<td>13 (21)</td>
<td>140 (57)</td>
<td>13 (21)</td>
<td>106 (64)</td>
<td>13 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>95 (39)</td>
<td>38 (63)</td>
<td>164 (52)</td>
<td>43 (76)</td>
<td>&lt;0.001</td>
<td>140 (57)</td>
<td>78 (71)</td>
<td>140 (57)</td>
<td>78 (71)</td>
<td>140 (57)</td>
<td>78 (71)</td>
<td>140 (57)</td>
<td>78 (71)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean cIMT, mm</td>
<td>0.99 (0.1)</td>
<td>0.98 (0.2)</td>
<td>1.0 (0.1)</td>
<td>0.97 (0.3)</td>
<td>&lt;0.001</td>
<td>1.0 (0.1)</td>
<td>0.98 (0.2)</td>
<td>1.0 (0.1)</td>
<td>0.98 (0.2)</td>
<td>1.0 (0.1)</td>
<td>0.97 (0.3)</td>
<td>1.0 (0.1)</td>
<td>0.98 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABI AS 0, %</td>
<td>0.04</td>
<td>0.29</td>
<td>0.29</td>
<td>0.29</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td>0.29</td>
<td>0.29</td>
<td>0.29</td>
<td>0.04</td>
<td>0.29</td>
<td>0.04</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AS 1, %</td>
<td>7 (32)</td>
<td>10 (46)</td>
<td>106 (33)</td>
<td>2 (3.6)</td>
<td>&lt;0.001</td>
<td>7 (32)</td>
<td>10 (46)</td>
<td>106 (33)</td>
<td>2 (3.6)</td>
<td>7 (32)</td>
<td>10 (46)</td>
<td>7 (32)</td>
<td>10 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AS 2, %</td>
<td>94 (39)</td>
<td>25 (41)</td>
<td>81 (25)</td>
<td>16 (28)</td>
<td>&lt;0.001</td>
<td>94 (39)</td>
<td>25 (41)</td>
<td>81 (25)</td>
<td>16 (28)</td>
<td>94 (39)</td>
<td>25 (41)</td>
<td>94 (39)</td>
<td>25 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AS 3, %</td>
<td>64 (26)</td>
<td>13 (21)</td>
<td>124 (39)</td>
<td>21 (37)</td>
<td>&lt;0.001</td>
<td>64 (26)</td>
<td>13 (21)</td>
<td>124 (39)</td>
<td>21 (37)</td>
<td>64 (26)</td>
<td>13 (21)</td>
<td>64 (26)</td>
<td>13 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AS 4, %</td>
<td>4 (1.7)</td>
<td>12 (20)</td>
<td>3 (1)</td>
<td>17 (30)</td>
<td>&lt;0.001</td>
<td>4 (1.7)</td>
<td>12 (20)</td>
<td>3 (1)</td>
<td>17 (30)</td>
<td>4 (1.7)</td>
<td>12 (20)</td>
<td>4 (1.7)</td>
<td>12 (20)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Atherosclerosis burden in those participants at low/intermediate risk

In subjects with cardiovascular events, diabetes mellitus or Score ≥5%, the performance of image-related techniques would be of no value, since they are at high risk. Therefore, we selected those participants with:

1. no previous cardiovascular events,
2. no diabetes mellitus and
3. Score ≤5%.

We identified 448 participants distributed as follows: 96 (55.2%) on dialysis, 36 (20.7%) in CKD Stages IV–V, 42 (24.1%) in CKD Stages I–III and 274 (32.2%) controls. Patients with atherosclerosis (AS 2/3) were significantly older in most of the groups studied. The distribution of current smokers, lipid profile, C-reactive protein and plasma glucose was not significantly different among groups. Furthermore, we did not find significant correlation between both C-reactive protein/body mass index and LDL cholesterol concentration.

We studied the distribution of atherosclerosis (AS) according to the classification of CKD and cardiovascular risk. Most of participants in the high-risk group had moderate to severe atherosclerosis (AS 2 or AS 3) which was not significantly different according to the stage of CKD (Figure 3). However, among those with low risk, we found that patients on dialysis presented a prevalence of atherosclerosis of 74%, which was significantly higher than in patients in CKD Stages I–III (40.5%, P < 0.05). When compared to the controls, the percentage was further reduced, since 38.9% of the control population at low risk presented moderate to severe atherosclerosis, P < 0.001. It is interesting to note that we identified 110 CKD patients (63.2%) classified as low to intermediate cardiovascular risk who presented AS 2/3.

Variables related to AS

The results of the multivariate analyses are displayed in Table 4. Once adjusted by CKD type, age was the strongest variable positively related to the presence of atherosclerosis. Similarly, the concentration of C-reactive protein was positively and significantly related to atherosclerosis. Gender was significantly related to atherosclerosis, women being the group with lower probability of moderate or severe atherosclerosis. This model has an area under the curve of 0.815, with a 95% CI [0.764, 0.866].

Discussion

Cardiovascular prevention based on risk factor approach has several limitations. It does not take into account differences in the pathophysiology of atherosclerosis, and furthermore, it does not evaluate the different impact on CVD risk according to different diseases (i.e. we similarly evaluated cardiovascular risk in healthy asymptomatic subjects, in comparison to CKD patients).

Our results confirmed the presence of a high proportion of subjects with atherosclerosis, a significantly higher proportion than in subjects with normal renal function, independent of the decade of age analysed. Furthermore, the diagnosis of atherosclerosis is especially prevalent in the group on dialysis (83.6%). This observation is not paral...
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>CKD-V/D (n = 193)</th>
<th>CKD/IV–V (n = 73)</th>
<th>CKD/I–III (n = 46)</th>
<th>CKD/IV–V (n = 26)</th>
<th>CKD/I–III (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.1 (11.3)</td>
<td>53.2 (16.4)*</td>
<td>74.1 (8.3)</td>
<td>60.4 (16.5)*</td>
<td>66.6 (10.1)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>66 (34)</td>
<td>21 (55)*</td>
<td>23 (32)</td>
<td>16 (62)*</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>66 (34)</td>
<td>9 (24)</td>
<td>25 (34)</td>
<td>8 (31)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>CVD history, n (%)</td>
<td>86 (46)</td>
<td>8 (21)</td>
<td>20 (27)</td>
<td>1 (4)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>29 (15)</td>
<td>10 (26)</td>
<td>10 (14)</td>
<td>2 (8)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>113 (59)</td>
<td>23 (61)</td>
<td>65 (89)</td>
<td>22 (85)</td>
<td>40 (87)</td>
</tr>
<tr>
<td>Statin therapy, n (%)</td>
<td>88 (46)</td>
<td>15 (39)</td>
<td>34 (47)</td>
<td>8 (31)</td>
<td>21 (46)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7 (4.7)</td>
<td>25.2 (4.6)</td>
<td>28.1 (4.4)</td>
<td>29.6 (6.9)</td>
<td>29.4 (4.4)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>155.7 (35.6)</td>
<td>159.7 (32.6)</td>
<td>166.9 (29.3)</td>
<td>187.7 (30.9)*</td>
<td>175.8 (28.9)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>46.9 (15.9)</td>
<td>50.4 (19.8)</td>
<td>53.4 (15.4)</td>
<td>55.5 (11.1)</td>
<td>56.4 (18.8)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>81.3 (30.8)</td>
<td>80.5 (28.9)</td>
<td>88.1 (22.9)</td>
<td>104.6 (24.5)*</td>
<td>95.0 (24.4)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>121.0 (92.0–165.0)</td>
<td>125.5 (84.3–166.0)</td>
<td>109.5 (85.0–146.8)</td>
<td>129.0 (109.5–150.8)</td>
<td>116.0 (85.0–157.0)</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>97.0 (86.0–124.0)</td>
<td>96.0 (84.0–136.5)</td>
<td>99.0 (89.0–109.5)</td>
<td>101.0 (91.0–116.0)</td>
<td>105.0 (99.3–118.8)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>7.0 (2.4–17.8)</td>
<td>4.0 (2.1–6.5)*</td>
<td>2.7 (2.0–6.3)</td>
<td>2.9 (1.9–4.7)</td>
<td>2.0 (2.0–4.0)</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>3.7 (0.4)</td>
<td>3.8 (0.3)</td>
<td>4.2 (0.3)</td>
<td>4.2 (0.3)</td>
<td>4.3 (0.2)</td>
</tr>
<tr>
<td>Microalbuminuria, mg/L</td>
<td>NA</td>
<td>NA</td>
<td>102.2 (93)*</td>
<td>60.3 (81)</td>
<td>59.7 (92)</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.8 (0.6)</td>
<td>8.7 (0.6)</td>
<td>9.1 (0.5)</td>
<td>9.2 (0.7)</td>
<td>9.3 (0.3)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>4.6 (1.4)</td>
<td>4.8 (1.2)</td>
<td>3.8 (0.5)</td>
<td>3.9 (0.7)</td>
<td>3.5 (0.5)</td>
</tr>
<tr>
<td>PTH</td>
<td>379 (1768)</td>
<td>343 (249)</td>
<td>176 (162)</td>
<td>157 (140)</td>
<td>44 (39)</td>
</tr>
<tr>
<td>Time on dialysis</td>
<td>31.1 (19.1–78.1)</td>
<td>26.8 (16.6–44.7)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*P-value <0.05 from a t-test for the comparison of means or, otherwise, from the Mann–Whitney test for the comparison of medians.

CKD-V/D, chronic kidney disease stage V on dialysis; CKD/IV–V, Stages IV–V without dialysis; CKD/I–III, Stages I–III; AS 2/3, atherosclerosis score 2 or 3; AS 0/1, atherosclerosis score 0 or 1.
Our results are in accordance with previously published studies. Rates of carotid atherosclerosis is higher in patients on dialysis [16,17] (carotid plaques were observed in 72% of the participants) than in pre-dialysis patients (prevalence of carotid plaques was 64% in previous studies) [18]. Mechanisms involved in this process pointed to a relevant role of inflammatory-related biomarkers (interleukin-6 and C-reactive protein) [19]. This was also observed in our study, supporting the concept of malnutrition–inflammation–atherosclerosis syndrome [20].

The NKF Task Force on CVD concluded that patients with CKD should be considered as high risk [21] and, consequently, the therapeutic targets (LDL cholesterol, blood pressure, etc.) should be managed accordingly. However, this strong recommendation is not acknowledged by either the European Journal of Cardiovascular Prevention and Rehabilitation 5 or the Adult Treatment Panel III Guidelines [22].

Our results indicate that diagnosing atherosclerosis might fill in the gap for detecting patients vulnerable to CVD and might be valuable in better individualizing cardiovascular status. Moreover, in the primary prevention of CVD in CKD, a shift in the paradigm, atherosclerosis detection rather than risk scoring alone, may be advocated.

However, several limitations should be acknowledged. The cross-sectional design of the study limits the strength of our findings and the AS should be tested prospectively to assess its potential predictive value using cardiovascular events as the end point. In this regard, our group is leading a multi-centre study to assess the predictive value of diagnosing atherosclerosis at different stages of CKD (National Observatorium in Atherosclerosis (NEFRONA) project, http://www.nefrona.es). Moreover, the identification of atherosclerosis is not always followed by cardiovascular events, and more precise diagnostic methods of vulnerable plaques should be explored in this high-risk, highly atherosclerotic population. With this in mind, the implementation of ultrasound contrast agents (microbubbles) to study neovascularization of plaques might be highly informative [23]. Further limitations of our study are that we did not study vascular calcification in our patients, since our aim was to study atherosclerosis or investigate whether a dissociation between risk scoring and atherosclerosis is present in different groups of subjects with CKD. Since there is no risk scoring based on surrogate markers for vascular calcification, introducing data relating to vascular calcification would be misleading.

The high prevalence of atherosclerosis should be followed up with therapeutic implications. One of the hallmarks in cardiovascular risk prediction is the control of

---

### Table 4. Multivariable analyses related to AS

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Standard error</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.59</td>
<td>0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD Stages IV-V vs CKD Stages I-III</td>
<td>0.18</td>
<td>0.39</td>
<td>1.20 (1.06–2.60)</td>
</tr>
<tr>
<td>CKD-V/D vs CKD Stages I-III</td>
<td>1.12</td>
<td>0.28</td>
<td>3.40 (1.72–6.77)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>-0.90</td>
<td>0.46</td>
<td>0.40 (0.22–0.70)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>0.03</td>
<td>0.01</td>
<td>1.04 (1.01–1.08)</td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Percentage of patients with atherosclerosis (AS 2/3) and LDL cholesterol ≤100 mg/dl. *P = 0.08 (CKD Stages I–III when compared to CKD/VD and CKD Stages IV–V); **P < 0.001 when comparing control vs CKD groups.

**Fig. 3.** Distribution of atherosclerosis (AS 2/3) according to cardiovascular risk and renal function. *P < 0.05 (CKD Stages I–III when compared to CKD/VD and CKD Stages IV–V); **P < 0.001 when comparing control vs CKD groups.
LDL cholesterol values. The results of published trials in haemodialysis (Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis (4D), Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) and AURORA) did not support the use of statins to reduce cardiovascular incidence [24–26]. However, it is certainly plausible that patients with CKD and with higher rates of atherosclerosis would be favoured by earlier treatments to halt future vascular events. In that sense, the Study of Heart and Renal Protection (SHARP) trial [27] will probably shed some light on this topic. It is remarkable, however, that we found 85 patients with atherosclerosis in whom the LDL cholesterol concentration was above 100 mg/dl. This is of particular interest in CKD Stages I–III because the tight control of risk factors would be more beneficial in the early stages of CKD. The presence of atherosclerosis is significantly higher at later stages of CKD [28], corresponding to two different areas of pathology. This is the reason why we studied our population taking into account the stage of CKD, both in univariate and multivariate analyses. Our results in such analyses indicate that those subjects in the early stages of CKD might be considered as the most important therapeutic target for controlling risk factors with the aim to reduce atherosclerosis burden.

Conclusion

In summary, the use of cardiovascular risk scoring (Score), in a population at different stages of CKD, underestimates the burden of atherosclerosis. These results may support a change in the paradigm prevention, from risk scoring to atherosclerosis detection, and further studies should be performed to evaluate the impact of this model in vascular events and mortality.

Acknowledgements. We are especially grateful to all the components of UDETMSA: Elisabet Samsó, Teresa Vidal and Josep M. Gutiérrez. Thanks to the research nurses and technicians: Teresa Vidal, Maria and Xavi Garcia, Vanesa Torres and Virtudes Maria. We also thank Nuria Sans and Oscar Muñoz for the database management and informatics support. B.C. and J.M.V. are supported by the Instituto de Salud Carlos III, Programa Miguel Servet. Sources of support ISCH-RETIC REDinREN.

Conflict of interest statement. None declared.

References

18. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Eval-
Cardiovascular risk factors underestimate atherosclerotic burden in CKD


Received for publication: 26.8.09; Accepted in revised form: 10.2.10