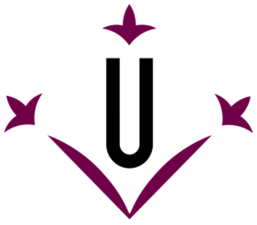

PREDICTORS OF SUBCLINICAL ATHEROMATOSIS PROGRESSION IN PATIENTS AT DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE AFTER TWO YEARS OF FOLLOW-UP. THE NEFRONA STUDY.

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Background and objectives: Ultrasonographic detection of subclinical atheromatosis is a noninvasive method predicting cardiovascular events. Risk factors predicting atheromatosis progression in chronic kidney disease (CKD) are unknown. Predictors of atheromatosis progression were evaluated in CKD patients.

Design, setting, participants, & measurements: Multicenter, prospective observational study in 1553 CKD patients (2009-2011). Carotid and femoral ultrasounds were performed at baseline and after 24 months. A subgroup of 476 CKD patients was also randomized to undergo ultrasound examination at 12 months. Progression of atheromatosis was defined as an increase in the number of plaque territories, analyzed by multivariate logistic regression.

Results: Prevalence of atheromatosis was 68.7% and progressed in 59.8% of patients after 24 months. CKD progression was associated with atheromatosis progression, suggesting a close association between pathologies. Variables significantly predicting atheromatosis progression, independently from CKD stages, were diabetes and two interactions of age with ferritin and plaque at baseline. Given that multiple interactions were found between CKD stage and age, phosphate, smoking, dyslipidemia, body mass index (BMI), systolic blood pressure (SBP), carotid intima-media thickness (cIMT), plaque at baseline, uric acid, cholesterol, 25-hydroxi-vitamin D and antiplatelet and phosphate binders use, the analysis was stratified by CKD stages. In stage 3, two interactions (age with phosphate and plaque at baseline) were found and smoking, diabetes, SBP, low levels of 25OH vitamin D, and no treatment with phosphate binders were positively associated with atheromatosis progression. In stage 4-5, three interactions (age with ferritin and plaque, and plaque with smoking) were found, and SBP was positively associated with atheromatosis progression. In dialysis, an interaction between BMI and 25OH vitamin D was found and age, dyslipidemia, cIMT, low cholesterol, ferritin and uric acid were positively associated with atheromatosis progression.

Conclusions: Atheromatosis progression affects more than half of CKD patients, and predictive factors differ depending on CKD stage.

INTRODUCTION

Cardiovascular disease is the main cause of death in chronic kidney disease (CKD) patients, in which cardiovascular death is a more likely outcome than progression to end-stage renal disease (ESRD).[1] Classical risk prediction equations underestimate cardiovascular disease risk in adults with CKD,[2;3] in which most events occur in patients with low-moderate risk.[4;5] Therefore, new tools for risk prediction in renal patients are needed. Arterial ultrasonography assessment of subclinical atheromatosis is a non-invasive imaging technique that could predict incidence of cardiovascular events better than traditional models.[6-9] It has been shown that increases in plaque burden have a strong predictive value assessing cardiovascular events in dialysis patients[10] and in the general population.[7] However, data on patients in early stages of CKD are scarce.[11]

Although numerous studies show an association between decreased kidney function and cardiovascular disease and mortality, mechanisms underlying this association are incompletely understood. This could be related to differences in cardiovascular events types and the associated factors amidst the progression of CKD. Thus, in early stages, there is a high mortality rate due to atherothrombotic ischemic events,[12-14] but in dialysis mortality is mainly caused by heart failure and sudden cardiac death.[15] Determining risk factors predicting atherosclerosis progression in every CKD stage could help to establish effective preventive measures to decrease cardiovascular disease in CKD patients.

Recently, baseline data from the NEFRONA[16] study have shown that patients in early CKD stages already have a higher prevalence of atheromatous plaques than those without CKD[17;18] and as previously shown, this prevalence is even

higher in advanced stages of CKD.[19-21] However, it is uncertain what the velocity of atheromatosis progression in CKD is[22;23] and little is known about the predictors of plaque progression in CKD patients. Only two studies have addressed this question, one with dialysis patients,[10] and another with a limited number of CKD stage 3-4 patients with a short interval ultrasound control.[22]

We present here the first longitudinal results from the NEFRONA study, regarding the risk factors predicting progression of atheromatosis in a large CKD patient population. Furthermore we assessed whether atheromatosis progression is associated with CKD progression.

METHODS

Design & study population

The protocol of the study was approved by the ethics committee of each hospital and all patients were included after signing informed consent. This research followed the principles of the Declaration of Helsinki. The design and objectives of the NEFRONA study have been published in detail.[24;25] Briefly, 2445 CKD patients (937 in CKD stage 3, 820 in stage 4-5 and 688 in dialysis) who were 18-75 years of age were enrolled from 81 Spanish hospitals between October 2009 and June 2011, with a scheduled follow-up visit after 24 months. Additionally, 476 CKD patients were randomly selected to undergo ultrasound examination also at 12 months. Patients from the NEFRONA study who had stenotic carotid plaque, ankle-brachial index (ABI) <0.7 at baseline, a cardiovascular event, received a renal allograft or died after the first ultrasound exploration were excluded from the follow-up visit.

Clinical data and Laboratory examinations

Current health status, medical history, former cardiovascular risk factors and drug use information was obtained at baseline. A physical examination was performed, consisting of anthropometric measures, standard vital tests and ABI measurements as previously described.[16] A pathological ABI was described as ≤ 0.9 or ≥ 1.4. Biochemical data were obtained from a routine fasting blood test within three months from the vascular study. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease Study formula (MDRD-4). Parathyroid hormone (PTH) levels in dialysis patients were corrected using a well-established method to avoid inter-method variability between different centers.[26]

Ultrasound Imaging

B-mode ultrasound of the carotid and femoral arteries was performed using the Vivid BT09 apparatus (General Electric) equipped with a 6-13 MHz broadband linear array probe as previously described.[27] An atheromatous plaque presence analysis was performed in 10 territories (both internal, bulb and common carotids, and both common and superficial femoral arteries) by a single reader in blinded fashion, using semi-automatic software (EchoPAC Dimension, General Electric Healthcare). To assess intraobserver reliability, a sample of 20 individuals was measured 3– 5 times on different days. A kappa coefficient of 1 was obtained for plaque assessment, indicating excellent intraobserver reliability. The reader was unaware of patients' clinical histories.

cIMT was only measured in common carotid regions without plaque and calculated as the average between left and right sides. The presence of

atheromatous plaques was defined as a cIMT > 1.5 mm protruding into the lumen, according to the ASE Consensus Statement[28] and the Mannheim cIMT Consensus.[29]

Evaluation of Progression

Atheromatosis progression was defined as an increase in the number of territories showing a plaque with respect to the baseline visit, as previously used in the MESA study.[30] Individuals doubling basal serum creatinine or starting renal replacement therapy were considered CKD progressive. Thus, patients in dialysis at baseline were excluded from this last variable.

Statistical analysis

Data are expressed as mean and standard deviation (SD) for quantitative variables and as relative frequencies for qualitative variables. In some quantitative variables in which nonlinear effects were detected, tertiles were used.

The relationship between potential risk factors with plaque progression at 24 months was analyzed by univariate and multivariate logistic regression. Chi-square or Mc Nemar tests were used to compare qualitative variables between progression and non-progression; the Mann-Whitney test was used for quantitative variables. Significant variables in univariate analyses and potential confounders were used to develop appropriate multivariate logistic regression models: age, sex, diabetes, smoking status, BMI, SBP, triglycerides, ferritin, cholesterol, dyslipidemia, uric acid, CKD stage, 25-OH-vitamin D, cIMT, plaque at baseline, statins treatment, antiplatelet drugs. A forward step procedure was used to build the multivariate model, including the variable showing maximum

contribution identifying those patients with 24-month atheromatosis progression, according to the likelihood ratio test (LRT). Those variables without a statistically significant contribution, but modifying in more than 10% the value of the coefficients (β) of any of the significant variables when removed from the model, were considered confounders and included in the final model. The model with the contributing or confounding variables was assessed for interactions of first and second order in a backward procedure to optimize AIC criterion. The contribution of the interactions identified by the former procedure was assessed by the LRT test in order to discard those interactions without a statistically significant contribution to the model. In case an explanatory variable showed multiple interactions with other covariates in the model, the analysis was stratified by that variable to facilitate interpretation. A statistical significance level of 0.05 was used.

All analyses were made using a standard statistical package (SPSS 21.0) and R program.

RESULTS

Baseline Characteristics

From the original NEFRONA study cohort (2445 CKD patients), 888 were excluded from the 24-month analysis. Namely, deaths (46), cardiovascular events (80), renal allografts during the 2 years (359) and second visit non-attendees (403). Finally, 1553 (709 CKD stage 3, 578 CKD 4&5 and 266 on dialysis) patients were included in the plaque progression analysis at 24 months because 4 presented plaque in all 10 territories at baseline. Furthermore, there were 476 patients who were also assessed after 12 months.

The cohort consisted of 61.6% men and mean age was 58.8 years. Of the patients, 29% were diabetic and 56% smokers. Baseline characteristics in participants according to CKD stages are detailed in **Table 1**. The percentage of men, smokers and the average age were higher among CKD stage 3 patients. Dialysis patients showed lower body mass index (BMI), systolic blood pressure (SBP), total cholesterol, LDL-cholesterol, corrected serum calcium and 1-25-dihydroxy vitamin D, whereas serum PTH and high-sensitive C-reactive protein (hsCRP) were higher. Atheromatous plaque prevalence was 68.7 % without significant differences between CKD stages. At baseline, 53% of patients had plaques in multiple territories and 16% had a single plaque; 37.2% had plaque in carotids and femorals, whereas 18.4% had plaque only in carotids and 13.1% exclusively in femorals. Prevalence of pathological ABI was 23.3%. The percentage of patients with pathological ABI was higher among patients in dialysis because of a high prevalence of ABI >1.4.

Analysis of progression at 24 months

The percentage of patients with plaque increased, from 68.6% to 81.4% at 24 months. Atheromatosis progression occurred in 59.8% of patients. Mean number of territories with plaque increased from 3.16 (SD=1.97) to 4.48 (SD=2.34).

Baseline potential factors predicting atheromatosis progression in univariate analysis are detailed in **Table 2.** In a multivariate regression model, assessing all significant predictors in the univariate analysis **(supplemental Table S1),** only diabetes and two interactions of first order (age with ferritin and the

presence of plaque at baseline) were independent predictors of atheromatosis progression with a similar effect across all CKD stages. Thus, the association of ferritin and plaque with the progression of atherosclerosis decreased with age. Significant interactions were found between CKD stage and age, phosphate, smoking, dyslipidemia, BMI, SBP, CCA-IMT, plaque at baseline, uric acid, cholesterol, 25-hydroxi-vitamin D and antiplatelet and phosphate binders use, three of them of second order**.** Therefore, to better understand risk factors for progression of atheromatosis, a multivariate model stratified by CKD Stages was built. This decision was justified by the existence of multiple interactions of CKD stage with other clinical variables, and also because many of those parameters show a very wide range when individuals from different CKD stages are pooled together. For instance, PTH or phosphate levels stay relatively stable in early stages, increasing very steeply in dialysis.

Atheromatosis progression at 24 months stratified by CKD stage

Risk factors of atheromatosis progression were analyzed in each CKD stage **(Table 3).** In stage 3, age, SBP, smoking, phosphate, the lack of phosphate binders use, diabetes, plaque presence and low 25OH vitamin D significantly predicted progression of atheromatosis. Two interactions of age with phosphate and plaque at baseline were also found. In CKD stage 4-5, age, SBP, smoking, plaque presence and ferritin significantly predicted the formation of new plaque, with significant interactions of age with plaque and ferritin, and of smoking with plaque**.** In dialysis, factors associated with new plaque formation were age, basal cIMT, dyslipidemia, ferritin and uric acid, whereas BMI, total cholesterol

and 25-OH-vitamin D were inversely associated. A significant interaction was found between vitamin D and BMI.

Presence of plaque at baseline, CKD progression and atheromatosis progression

In contrast to patients with plaque at baseline, atheromatosis progression in patients free from disease at baseline was very low (**Figure 1**). Furthermore, bivariate analysis shows that the percentage of patients with atheromatosis progression was higher in the group with CKD progression (**Table 2**). **Figure 2** shows that progression of atheromatosis was significantly more frequent in patients with CKD progression. **Figure 3** shows the percentage of patients with atheromatosis progression according to CKD progression and the presence of plaques at baseline. Almost 80% of patients in which CKD progressed and had plaque at baseline experienced aggravation of atheromatosis. At the other end, around 60% of patients in which CKD did not progress and were free of plaques at baseline, did not suffer an increase in atheromatous burden. Spearman correlation between progressors in both CKD and atheromatosis was positive and statistically significant (s=0.1, p=0.004).

Atheromatosis progression at 12 months

In one patient subgroup, progression of atheromatosis was also evaluated after 12 months from the first visit and plaque progression was observed in 47% of the patients. Of those, 54% of them progressed even more at 24 months. Of the

non-progressors at 12 months, 38% progressed at 24 months. (Supplemental **Figure S1**).

DISCUSSION

In this work we analyze atheromatosis progression and the factors predicting it in a subpopulation of the NEFRONA study who did not suffer a cardiovascular event during the 24 months of follow-up. Our main findings are: 1) In CKD there is a high prevalence of patients with atheromatous plaque in carotid and/or femoral territories, but about 30% are free from atheromatosis. Moreover, in about 40% of patients atheromatosis progression is absent after 2 years. 2) The only variables with a homogeneous association with the progression of plaque across CKD stages were the presence of diabetes and two interactions of age with ferritin and the presence of plaque at baseline. 3) Apart from those variables, risk factors predicting atheromatosis progression are different depending on the CKD stage. 4) The progression of atheromatosis is associated with the progression of CKD.

The data also show that, although this is a population with high cardiovascular risk, a significant proportion of patients are free from atheromatosis.–Interestingly, in these particular patients without plaque at baseline, atheromatosis progression is slow or nonexistent, suggesting a phenotype of individuals ‘protected’ from the disease. Identifying the phenotypic characteristics in these patients is of great interest to the study of the pathogenesis of atheromatosis.

The progression of atheromatosis was assessed by quantifying the number of carotid and femoral territories with plaque, as previously reported in other studies.[30] Quantifying did not require special software (for a more sophisticated analysis such as plaque area or volume) and also predicts cardiovascular events more accurately than IMT.[9] Benedetto et al showed that progression of atheromatosis is a better predictor of cardiovascular events than the baseline number of plaques in a cohort of ESRD patients,[10] indicating that monitoring the evolution of plaque burden adds independent prognostic information. One novelty included in our study is the analysis of femoral arteries, which are not routinely explored. Our results indicate that if only carotid territories had been explored, the presence of plaque would have been under-diagnosed in around 13% of patients. Although exploration of the femoral territories may cause discomfort to the patient, it does not increase the cost of the exploration and provides valuable information for a significant proportion of patients.

Interestingly, it was found that CKD progression is associated with atheromatosis progression. Although both occur concurrently and we cannot use one as a predictor of the other, the results demonstrate that both pathologies are closely related and that patients who progress in one are more likely to progress in the other, independently of other factors.

The multivariate logistic regression model to predict progression of atheromatosis in the whole population showed traditional risk factors similar to the results of the MESA[30], the Rotterdam[31] and TromsØ studies[32], although we found multiple interactions between CKD stages and the other clinical variables. However, being diabetic predicted atheromatosis progression independently of the CKD stage. Furthermore, having plaque at baseline and high levels of

ferritin also predicted the progression of atheromatosis independently of the degree of renal function, although this effect is modified by age, being lower in older patients.

The stratified analysis showed that in CKD stage 3, SBP, smoking and diabetes predicted progression of atheromatosis. Therefore, in early stages of CKD, we can use classic cardiovascular risk factors to predict plaque progression. Additionally, high phosphate levels and low 25-OH vitamin D levels were also predictors of atheromatosis progression. Indeed, a potential role for phosphate and 25-OH vitamin D levels has been previously suggested in the progression of atherosclerosis.[33-37] Furthermore, a significant interaction between phosphate levels and age was found, showing that when phosphate levels are over 3.6 mg/dL, the association with age is much stronger. This is consistent with previous results only showing a phosphate binder benefit in older patients[38]. However, in our study, patients treated with phosphate binders seemed to have lower odds of atheromatosis progression, independently of their age. On the other hand, the association with age is minor in patients with plaque already at baseline because this in itself is a high risk condition. In CKD stages 4-5 new risk factors appear, like the ferritin levels. Thus, it seems that inflammation starts to play a role in atheromatous plaque progression in predialysis stages. In dialysis patients, risk factors for atheromatosis progression are completely different. A paradoxical association was observed with cholesterol levels. However, history of dyslipidemia still persists as a risk factor, suggesting that actual low cholesterol levels could be a reflection of a state of malnutrition, as reflected by a better prognosis in patients with a higher BMI. Uric acid appears as a predictor of atheromatosis progression, agreeing with previous results.[39;40]

Inflammation, estimated by high ferritin levels, persists as an important risk factor for atheromatosis. Low vitamin D levels are also predictors of plaque progression, confirming previous experimental studies showing the effect of a vitamin D deficit on atheromatosis.[41-43] A significant interaction between vitamin D and BMI was also found. Only patients with low to moderate BMI showed lower odds of progression with high vitamin D levels. The results also confirm that higher cIMT emerges as a predictor of atheromatosis progression in this group of patients.

The main strength of this study is the large number of patients with longitudinal observations, which allows us to make predictive associations between multiple factors and atheromatosis progression and to adjust for multiple confounders. Another strength is that the vascular exploration was performed by the same team and evaluated by a single reader.

This study also has several limitations. First, the large number of dropouts lowers the statistical power of the study. Given that only patients without cardiovascular events were evaluated at baseline and follow-up and most of the dropouts were either patients receiving a transplant or patients who died, a subpopulation with intermediate health status was probably being analyzed. In addition, plaque volume and density were not measured. Finally, FGF23 levels were lacking, which could have been mediating the effects of high phosphate in atheromatosis and only a small portion of patients had levels of proteinuria.

In summary, data presented here demonstrate the validity of the determination of atheroma plaque presence by arterial ultrasound as a powerful tool to predict atheromatosis progression in CKD patients. The factors predicting

atheromatosis progression in each CKD stage are different. Furthermore, CKD progression and atheromatosis progression are closely associated.

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Table 1. Main Baseline Characteristics in Participants according to CKD stage (n=1553). Quantitative data are expressed as mean and standard deviation (SD) or median, (p25, p75) depending on the normality of the distribution. Qualitative variables are expressed as N (%). [a]Abdominal obesity: waist circumference ≥ 102 cm (male) or ≥ 88 (female), not measured in peritoneal dialysis patients. [b]HbA1c was measured only in diabetic patients. [c]Urine Albumin-to-Creatinine Ratio (UACR) and CKD progression not measured in dialysis patients. [d]In patients with plaque at baseline. [e]cIMT: Common carotid artery intima media thickness. *p* values reflect differences between CKD stages.

	CKD 3	CKD 4-5	CKD 5D	p
N	709 (46)	578 (37)	266 (17)	
Males	481 (67.8)	328 (56.7)	147 (55.3)	<0.001
Age (years)	63 (56, 69)	61 (51, 68)	55 (44, 66)	<0.001
Race (white)	700 (98.7)	562 (97.2)	247 (92.9)	<0.001
Medical history				
Smoker	413 (58.3)	317 (58.4)	139 (52.2)	<0.001
Diabetes	186 (26.2)	158 (27.3)	40 (15)	<0.001
Hypertension	645 (91)	550 (95.2)	232 (87.2)	<0.001
Dyslipidemia	506 (71.4)	409 (70.8)	151 (56.8)	<0.001
Etiology of renal disease				
Vascular disease	217 (37.2)	94 (18.4)	9 (11)	<0.001
Diabetic Nephropathy	84 (14.4)	90 (17.6)	25 (11.5)	0.12
Others	282 (48.4)	326 (63.9)	169 (77.5)	<0.001
Body mass index (kg/m^2)	28.8 (26, 31.8)	27.7 (24.9, 32)	26.1 (23.1, 30)	<0.001
Abdominal obesity[a]	142.5 (52.6)	294 (51.9)	84 (45.4)[a]	0.21
Systolic BP (mmHg)	142.4 (19.5)	143.9 (20.5)	139.4 (23)	0.03
Diastolic BP (mmHg)	81.9 (10.07)	82 (11.1)	80.5 (13.5)	0.33
Pulse pressure (mmHg)	60.5 (15.8)	61.9 (18)	58.8 (18.6)	0.10
Time on dialysis (months)			16.6 (7, 33.8)	--
Total Cholesterol (gr/dL)	188.3 (36.9)	177.9 (37.1)	165.03 (45.2)	<0.001
LDL Cholesterol (gr/dL)	111 (32.5)	101.1 (32.3)	90.9 (34.7)	<0.001
HDL Cholesterol (gr/dL)	48 (40, 58)	47 (37.8, 59)	45 (36.4, 56)	<0.001
Non-HDL Cholesterol (mg/dL)	138.2 (34.8)	128.9 (35.1)	118.8 (43.3)	<0.001
Triglycerides (mg/dL)	122 (92, 174)	125 (91, 171)	121 (90, 170)	0.95
HbA1c (%)[b]	6 (5.5, 6.7)	5.9 (5.4, 6.8)	5.1 (4.8, 5.8)	<0.001
Albumin (gr/dL)	4.2 (0.4)	4.1 (0.4)	3.8 (0.4)	<0.001
Hematocrit (%)	41.6 (4.7)	37.4 (4.2)	35.8 (4.4)	<0.001
Ferritin (mg/dL)	110.1 (60, 210)	148 (74, 268)	316 (159, 474)	<0.001
Corrected calcium (mg/dL)	9.27 (0.5)	9.2 (0.5)	9.1 (0.7)	<0.001
Phosphate (mg/dL)	3.3 (0.5)	4 (0.7)	4.8 (1.2)	<0.001
PTH (pg/mL)	68.7 (49.2, 98)	137 (91.6, 212)	226 (145, 344)	<0.001
Uric Acid (mg/dL)	6.79 (1.5)	6.99 (1.6)	6.02 (1.4)	<0.001
25-hydroxy vitamin D (pg/mL)	15.2 (11.8,20.1)	15.7 (11.3, 19.9)	13.6 (10, 18.9)	<0.001
1-25-hydroxy vitamin D (ng/mL)	19.3(14, 26.3)	15.3 (10.1, 22.2)	6.2 (4.1, 9.9)	<0.001
hs C-Reactive Protein (mg/L)	1.8 (0.9, 3.7)	1.72 (0.84, 3.98)	2.5 (0.99, 6.6)	0.01
UACR (mg/g)[c]	51.5 (7.6, 264)	173.4 (30, 677)	na[c]	<0.001
CKD progression	12 (1.7)	146 (25.3)	na	<0.001
Atheromatosis progression	418 (59)	344 (59.5)	168 (63.2)	0.47
Treatments				
Antihypertensive	655 (92.4)	560 (96.9)	194 (72.9)	<0.001
Statins	425 (67.8)	370 (64)	136 (51.1)	<0.001
Phosphate binders	38 (5.4)	186 (32.2)	210 (78.9)	<0.001
Vitamin D	128 (18.1)	281 (48.6)	136 (51.1)	<0.001
Antiplatelet drugs	153 (21.6)	134 (23.2)	76 (28.6)	0.07
Plaque presence	495 (69.8)	385 (66.6)	186 (69.9)	0.41
Multiple plaques[d]	363 (73.3)	310 (80.5)	143 (76.9)	0.12
Number of territories with plaque[d]	3 (1, 4)	3 (2, 4)	3 (2, 4.3)	0.88
cIMT (mm)[e]	0.74 (0.14)	0.7 (0.1)	0.7 (0.1)	<0.001
Pathologic Ankle-Brachial index	147 (20.7)	126 (21.9)	88 (33.2)	<0.001
ABI ≤ 0.9	109 (15.4)	76 (13.2)	30 (11.3)	0.22
ABI ≥ 1.4	38 (5.4)	50 (8.7)	58 (21.9)	<0.001

Table 2. Baseline factors associated with progression of atheromatosis in all patients (n=1553). Quantitative data are expressed as mean and standard deviation (SD), or median, (p25, p75) depending on the normality of the distribution. Qualitative variables are expressed as N (%). [a]Abdominal obesity: waist circumference ≥ 102 cm (male) or ≥ 88 (female), not measured in Peritoneal dialysis patients. [b]HbA1c was measured only in diabetic patients. [c]Urine Albumin-to-Creatinine Ratio (UACR): not measured in dialysis patients. [d]In patients with plaque at baseline. [e]cIMT: Common carotid artery intima media thickness.

	ATHEROMATOSIS PROGRESSION	NO ATHEROMATOSIS PROGRESSION	p
N	930 (59.8)	623 (40.1)	
Males	608 (67.8)	348 (56.7)	<0.001
Age (years)	64 (56, 70)	57 (43, 66)	<0.001
Race (white)	914 (98.3)	595 (95.5)	<0.001
Medical history			
Smoker	561 (60.3)	308 (49.4)	<0.001
Hypertension	877 (94.3)	550 (88.3)	<0.001
Diabetes	278 (29.9)	106 (17)	<0.001
Dyslipidemia	674 (72.5)	392 (62.9)	<0.001
Etiology of renal disease			
Vascular disease	210 (27.1)	125 (23.3)	0.12
Diabetic Nephropathy	143 (18.5)	56 (10.4)	<0.001
Others	422 (54.5)	355 (66.2)	<0.001
Body mass index (kg/m^2)	28.5 (25.4, 31.8)	27.7 (24.5, 31.6)	<0.001
Abdominal obesity[a]	469 (53.8)	287 (48.1)	0.03
Systolic BP (mmHg)	144.8 (21.2)	138.9 (19)	<0.001
Diastolic BP (mmHg)	81.57 (11.4)	81.96 (10.7)	<0.001
Pulse pressure (mmHg)	63.29 (18.0)	57.01(15.2)	<0.001
CKD stages			0.48
Stage 3	418 (44.9)	291 (46.7)	
Stage 4-5	344 (37)	234 (37.6)	
Stage 5D	168 (18.1)	98 (15.7)	
Time on dialysis (months)	17.5 (6.7, 33.4)	16.3 (7.4, 34.2)	0.82
Total Cholesterol (gr/dL)	179.9 (39.8)	181.8 (38.6)	0.27
LDL Cholesterol (gr/dL)	102.9 (33.5)	105.2 (33.7)	0.26
HDL Cholesterol (gr/dL)	49 (15.2)	50.1 (14.7)	0.11
Non-HDL Cholesterol (mg/dL)	131.1 (38.3)	131.7 (35.4)	0.49
Triglycerides (mg/dL)	126 (94, 176.5)	118 (86, 165)	<0.001
HbA1c (%)[b]	6 (5.4, 6.7)	5.7 (5.2, 6.4)	<0.001
Albumin (gr/dL)	4.2 (0.4)	4.1 (0.4)	0.93
Hematocrit (%)	39 (5)	39.2 (5.1)	0.51
Ferritin (mg/dL)	160.1 (78, 313.2)	136.2 (66.5, 242)	<0.001
Corrected calcium (mg/dL)	9.2 (0.5)	9.2 (0.5)	0.10
Phosphate (mg/dL)	3.9 (0.9)	3.8 (0.9)	0.42
PTH (pg/mL)	114.8 (68.4, 193.8)	101 (62.3, 186)	0.08
Uric acid (mg/dL)	6.71 (1.6)	6.78 (1.6)	0.29
25-hydroxy vitamin D (pg/mL)	14.7 (11.2, 19.1)	15.9 (11.9, 20.7)	<0.001
1-25-hydroxy vitamin D (ng/mL)	16.1 (10.3, 22.9)	15.6 (10.1, 22.7)	0.83
hs C-Reactive Protein (mg/L)	2 (0.96, 4.7)	1.77 (0.8, 3.8)	<0.001
UACR (mg/g)[c]	92.5 (12, 438.6)	100.8 (13.7, 404)	0.83
Treatments			
Antihypertensive	857 (92.2)	552 (88.6)	0.02
Hypolipemiant	578 (69.5)	353 (60.5)	<0.001
Phosphate binders	257 (27.6)	177 (28.4)	0.74
Vitamin D	334 (35.9)	211 (33.9)	0.41
Antiplatelet drugs	238 (25.6)	125 (20.1)	0.01
Plaque at baseline	733 (78.8)	333 (53.5)	<0.001
Multiple plaques[d]	562 (76.6)	254 (76.2)	0.89
Number of territories with plaque[d]	2 (1, 4)	1 (0, 3)	0.43
cIMT (mm)[e]	0.74 (0.14)	0.67 (0.13)	<0.001
Pathologic Ankle-Brachial index	226 (24.3)	135 (21.7)	0.24
ITB ≤ 0.9	128 (13.8)	87 (14)	0.90
ITB ≥ 1.4	98 (10.5)	48 (7.7)	0.06
CKD progression	109 (14.3)	49 (9.4)	<0.001

Table 3. Multivariate logistic regression to model plaque progression at 24 months stratified by CKD stage 3, 4-5 and 5D. Results are expressed as *OR (Exponential β for independent variables with interactions) and 95% Confidence interval (95% CI). The following variables were introduced to build multivariate models by CKD stages because they were significant on bivariate testing or potential confounders: sex, CKD stage, age (decades), diabetes, smoking, dyslipidemia, SBP ≥ 150 mmHg (highest tertile in CKD stage 3), Pulse pressure, BMI, basal plaque, cIMT, ferritin > 220 mg/dL (Highest tertile in CKD Stage 4-5), uric acid, CRP, Total cholesterol> 180 mg/dL (the level of 180 was selected based in clinical criteria), LDL-cholesterol, hematocrit, statins, antiplatelet drugs, triglycerides, 25-OH-vitamin D (ln 25-0H-vitamin D for interactions and CKD Stage 4-5 and 5D, and 25-OH-vitamin D ≥ 18.1 (Vitamin D highest tertile in CKD Stage 3), (P highest tertile in CKD stage 3 > 3.6 mg/dL), PTH. Only significant variables in multivariate analysis in each group of CKD were included in the final model. The Exp β and p values of the rest of the variables are the values obtained if added to the final model. **CKD stage 3**. Hosmer Lemeshow= 0.46, AUC= 0.72. **CKD stage 4-5**. Hosmer Lemeshow= 0.82 AUC= 0.74. **CKD stage 5D**. Hosmer Lemeshow=0.16, AUC=0.83.

	CKD Stage 3		*CKD Stage 4-5*		*CKD Stage 5D*	
	OR* (95% CI)	p-value	OR* (95% CI)	p-value	OR* (95% CI)	p-value
Age (decades)	**1.65 (1.24-2.25)**	**<0.001**	**1.95 (1.43-2.75)**	**<0.001**	**1.48 (1.07-2.06)***	**0.02**
Smoking (current & former vs no)	**1.77 (1.24-2.55)**	**<0.001**	**3.95 (1.91-8.50)**	**<0.001**	1.32 (0.64-2.74)	0.45
Diabetes (yes vs. no)	**1.59 (1.06-2.41)***	**0.03**	1.45 (0.92-2.31)	0.11	2.37 (0.66-10.74)	0.22
SBP ≥ 150 mmHg	**1.46 (1.01-2.12)***	**0.04**	**2.84 (1.86-4.39)***	**<0.001**	0.64 (0.29-1.40)	0.26
P >3.6 mg/dL	**1.62 (1.09-2.43)**	**0.02**	0.84 (0.54-1.30)	0.44	0.80 (0.28-2.17)	0.66
Phosphate binders use (yes vs. no)	**0.42 (0.19-0.88)***	**0.02**	0.78 (0.51-1.19)	0.25	1.38 (0.56-3.34)	0.48
25-OH-vitamin D (pg/mL)	**0.62 (0.43-0.89)***	**0.01**	1.34 (0.82-2.20)	0.24	**0.08 (0.01-0.47)**	**0.01**
Plaque at baseline (yes vs. no)	1.33 (0.85-2.06)	0.21	**3.16 (1.68-6.02)**	**<0.001**	1.20 (0.50-2.82)	0.67
Age*P	**1.70 (1.16-2.54)**	**0.01**	0.95 (0.63-1.42)	0.22	1.02 (0.44-2.09)	0.95
Age*Plaque at baseline	**0.66 (0.45-0.96)**	**0.03**	**0.62 (0.41-0.93)**	**0.02**	0.58 (0.29-1.11)	0.11
Ferritin > 220 ng/mL	1.33 (0.82-2.18)	0.25	1.37 (0.89-2.14)	0.16	**2.54 (1.20-5.52)***	**0.02**
Age*Ferritin > 220 ng/mL	0.91 (0.58-1.49)	0.69	**0.66 (0.45-0.97)**	**0.04**	1.22 (0.70-2.11)	0.95
Smoking*Plaque at baseline	0.45 (0.19-1.02)	0.06	**0.32 (0.13-0.78)**	**0.01**	2.75 (0.60-13.12)	0.20
BMI (kg/m^2)	0.99 (0.96-1.03)	0.76	1.01 (0.97-1.05)	0.67	**0.79 (0.66-0.93)**	**0.01**
Dyslipidemia (yes vs. no)	1.27 (0.86-1.85)	0.23	1.39 (0.89-2.15)	0.14	**5.14 (2.34-12.01)***	**<0.001**
Cholesterol > 180 mg/dL	1.15 (0.81-1.63)	0.45	1.06 (0.71-1.6)	0.77	**0.31 (0.13-0.70)***	**0.01**
Uric acid (mg/dL)	1.08 (0.96-1.21)	0.22	1.02 (0.91-1.16)	0.72	**1.38 (1.06-1.84)***	**0.02**
cIMT (mm)	1.07 (0.93-1.23)	0.37	1.12 (0.95-1.33)	0.18	**1.66 (1.22-2.32)***	**<0.001**
Ln 25-OH-vitamin D*BMI	1.01 (0.94-1.09)	0.82	0.95 (0.87-1.03)	0.22	**1.16 (1.02-1.33)**	**0.02**

FIGURE LEGENDS

Figure 1. Boxplot showing the number of territories with plaque at baseline and after 24 months of follow-up according to the presence of plaque at baseline. The highest whisker indicates the last value that is less than or equal to the result of the standard formula p75+1.5*IQR. Circles or stars represent readings that are outliers or far outliers, respectively (defined as higher than p75 + 1.5*IQR or p75 + 3*IQR, respectively). $p<0.001$ between progression in patients with plaque at baseline vs. progression in patients without plaque at baseline.

Figure 2. Percentage and CI (95%) of patients that showed atheromatosis progression according to CKD progression after 24 months. $p<0.001$

Figure 3. Percentage of patients with progression of atheromatosis over 24 months according to basal plaque and CKD progression in CKD stages 3 and 4-5. $p<0.001$ between progression in patients with neither CKD progression nor plaque at baseline and progression in patients with CKD progression and plaque at baseline.

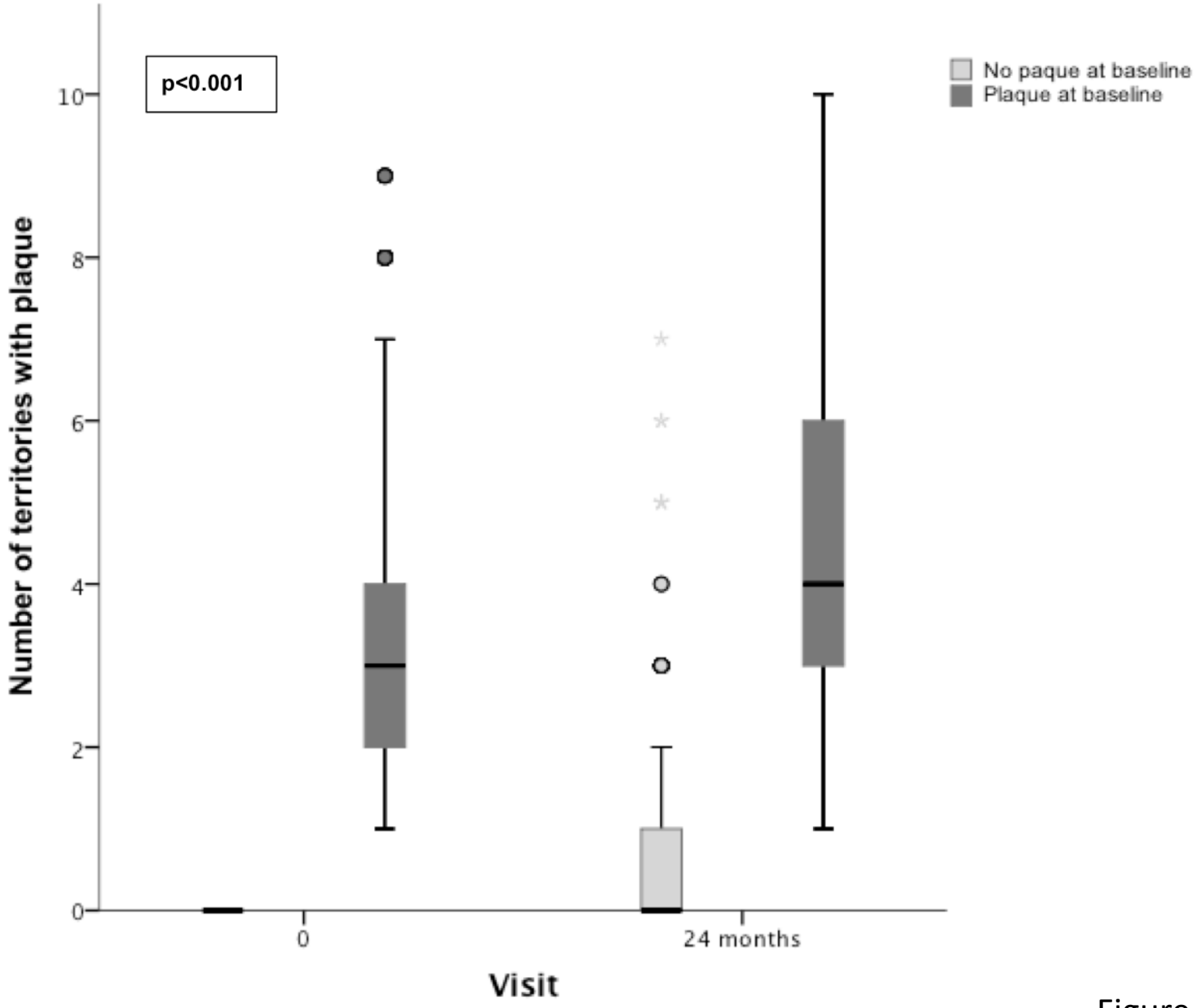
p<0.001
No paque at baseline
Plaque at baseline
Number of territories with plaque
10
8
6
4
2
0
0
24 months
Visit

Figure 1

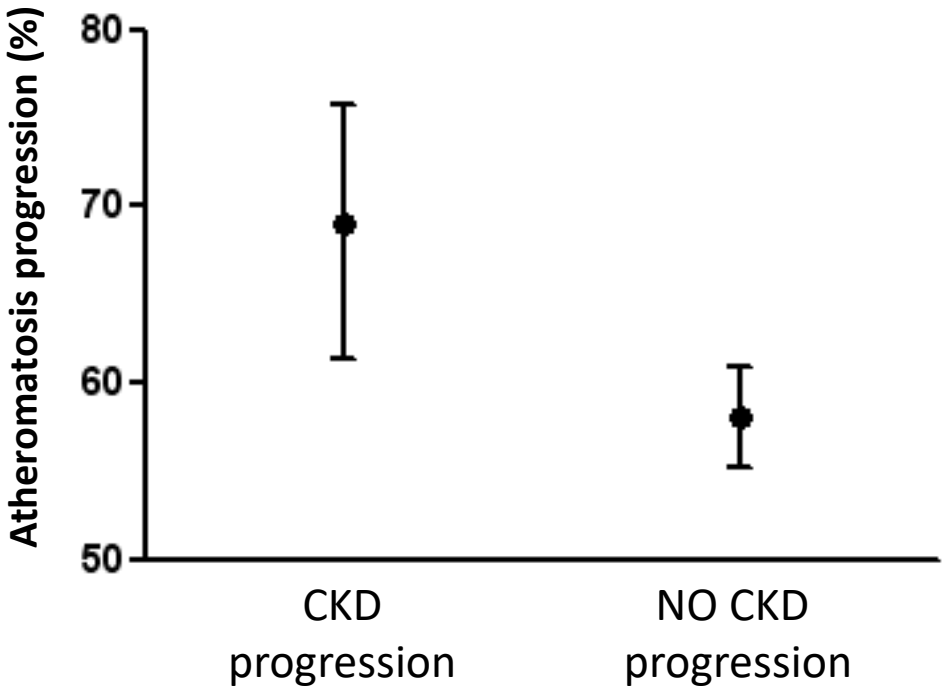
Atheromatosis progression (%)
80
70
60
50
CKD progression
NO CKD progression

Figure 2

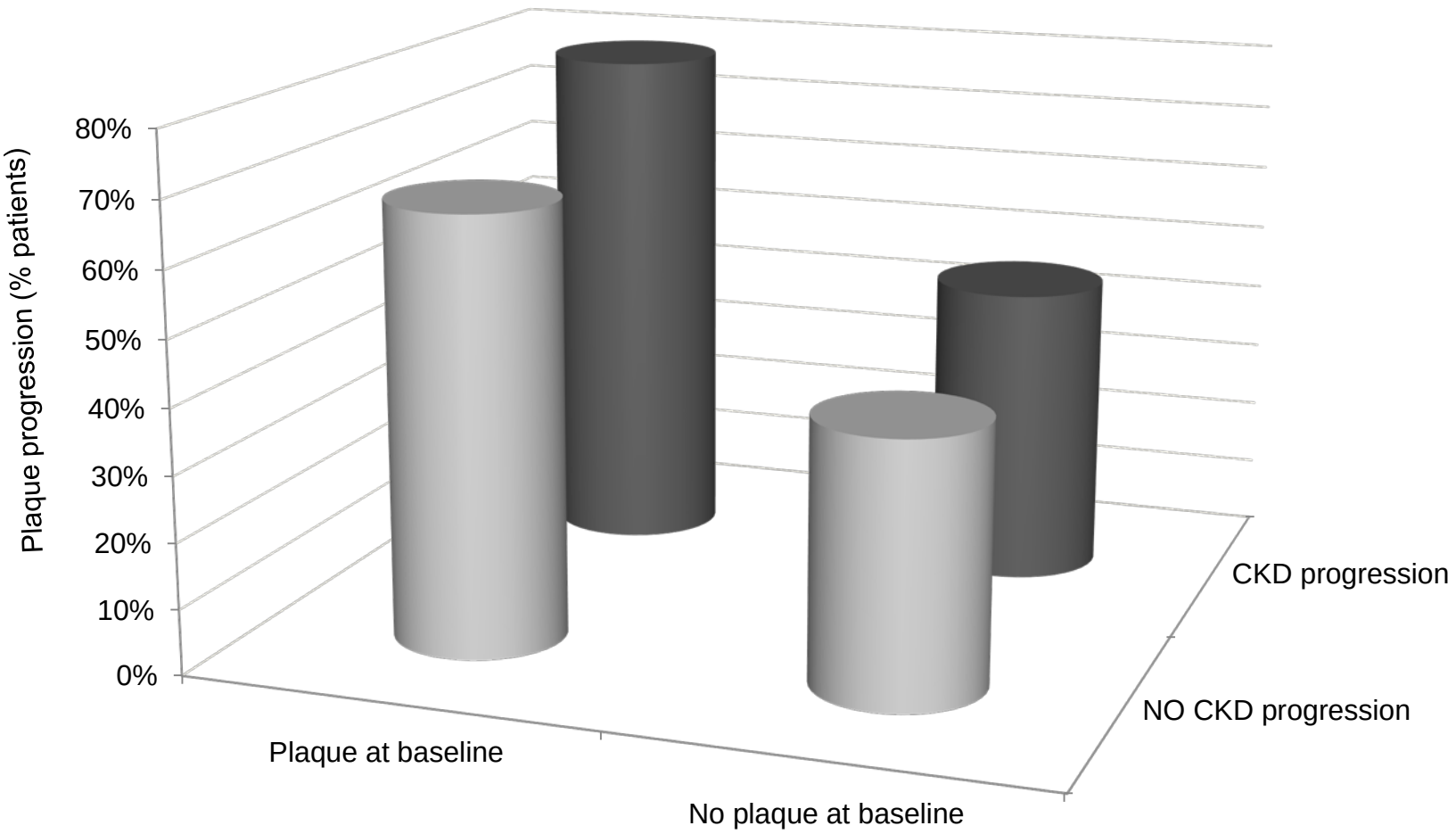
Plaque progression (% patients)
80%
70%
60%
50%
40%
30%
20%
10%
0%
Plaque at baseline
No plaque at baseline
CKD progression
NO CKD progression

Figure 3