KLOTHO GENE POLYMORPHISMS ARE ASSOCIATED WITH PROGRESSION OF ATHEROMATOSIS IN PATIENTS WITH CKD. RESULTS OF TWO YEARS FOLLOW-UP OF THE NEFRONA COHORT.

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BACKGROUND

Ultrasonographic detection of progression of subclinical atheromatous disease (atheromatosis) is a noninvasive method that predicts cardiovascular events. Low serum levels and also different polymorphisms of human klotho gene have been related to the prevalence of cardiovascular diseases, but the mechanism of this relationship is still unknown. We analyze the association of Klotho polymorphisms and subclinical atheromatosis progression in the NEFRONA cohort.

METHODS

Multicenter, prospective and observational study of 1553 CKD patients (709 stage 3, 578 stages 4-5 and 266 on dialysis) without previous cardiovascular events from the NEFRONA cohort. A carotid and femoral ultrasound examination was performed at baseline and 24 months follow-up. A unique reader performed the evaluation of the images. Progression of AD was defined as formation of plaques in previously vascular healthy territories. CKD progression was defined as doubling of serum creatinine or the onset of dialysis. The statistical level of significance was fixed to 0.05.

RESULTS

Prevalence of atheromatous plaque at baseline was 69 % and progression of AD occurred in 60% patients after 24 months, a higher rate of progression was observed in patients with plaque at baseline **(Figure 1)**. Main baseline characteristics of Participants stratified by plaque at baseline (n=1553) are shown in **Table 1.** Variables significantly and positively predicting AD progression in multivariate regression analysis are different according to the presence of plaque at baseline **(Table 2)**. Two polymorphisms of klotho and IMT were associated with progression of atheromatosis in all patient; Factors associated with atheromatosis progression in patients without plaque at baseline was age and in patients with plaque were diabetes and PTH.

Fig. 1 Progression of plaque after 24 months stratified by plaque at baseline.

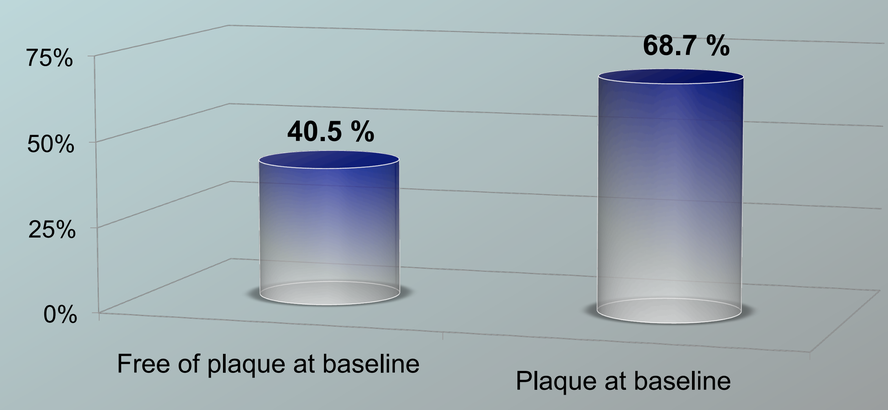

Table 1. Main Baseline Characteristics in Participants by plaque at baseline (n=1553).

	Free of plaque at baseline	Plaque at baseline	p
N	487	1066	
Males (%)	47.6	67.9	< 0.001
Age (years)	49.9±13.9	62.5±9.1	< 0.001
Smoker (%)	45.2	60.9	< 0.001
Diabetes (%)	14.6	29.4	< 0.001
Hypertension (%)	87.9	93.7	< 0.001
Dyslipidemia (%)	60.8	72.2	< 0.001
ccIMT (mm)	0.64±0.1	0.76±0.14	< 0.001
ABI ≤ 0.9 or ≥ 1.4 (%)	16.7	26.3	<0.001
PTH (pg/mL)	159.5±190.6	156.6±154	0.795

ccIMT: Common Carotid Artery Intima Media Thickness. ABI: Ankle-Brachial Index

Table 2 Multivariate logistic regression to model plaque progression at 24 months stratified by plaque at baseline.

	Free of plaque at baseline		Plaque at baseline	
	β (S.E.)	p-value	β (S.E.)	p-value
Age (decades)	1.46	0.007		
CCA-IMT (mm)	1.79	0.022	1.18	0.006
Klotho rs385564 recessive	0.41	0.015		
Diabetes			2.01	0.001
PTH (pg/mL) > 79 vs. <79			1.37	0.002
Klotho rs567170 recessive			0.75	0.019

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, Pulse pressure, BMI, basal plaque, cIMT, ferritin, uric acid, CRP, Total cholesterol> 180 mg/dL[c] (the level of 180 was selected based in clinical criteria), LDL-cholesterol, hematocrit, statins, antiplatelet drugs, triglycerides, 25-OH-vitamin D, Phosphorous. PTH. Finally, only significant variables in multivariate analysis in each group of plaque or no plaque were included in the final model. **Free of plaque at baseline**. Hosmer Lemeshow=0.175, AUC=0.763 . **Plaque at baseline**. Hosmer Lemeshow=0.937, AUC=0.629.

CONCLUSIONS

Klotho gene polymorphisms are associated with progression of atheromatosis in patients with CKD.

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