Diabetic nephropathy is an independent risk factor for severe silent atheromatous disease. The NEFRONA Study

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BACKGROUND

Chronic kidney disease (CKD) and diabetes mellitus are well known risk factors for cardiovascular (CV) events and disease. However the association of different etiologies of primary renal disease such as diabetic nephropathy (DN) or vascular nephropathies (VN) with an increased risk of silent atheromatous disease (AD) has been scarcely evaluated.

METHODS

In the prospective Spanish multicenter cohort NEFRONA study (1), we assessed 3040 subjects without any CV event: 2481 patients with CKD stages 2 to 5 and 559 controls with normal kidney function. Patients were divided according with primary renal disease in 4 groups: Diabetic Nephropathy , Vascular Nephropathy, Systemic/Glomerular disease and other causes.

B mode and Doppler ultrasonography analysis of the carotid arteries were performed to measure intima media thickness (IMT, mm) and the presence of plaques. AD was scored according with the ultrasonography findings and the ankle-arm index (AAI) into 2 large groups; absence or incipient-AD (AAI>0.7 and no carotid plaques) and severe-AD (AAI<0.7 or carotid plaques). Various clinical and laboratory parameters related to CV risk were also determined.

RESULTS

Etiology of Renal Disease	Diabetic	Vascular	Systemic/Glom	Others	Healthy Controls	p
N	357	487	463	1174	559	
Age	59.1 ± 12.3	63.3 ± 9.4	52.4± 13	56.7 ± 12.6	54.2 ± 11	ND
Gender (% male)	64.7	66.5	63.9	58.7	53.3	ND
Smoking (%)	20.7	18.1	21.0	19.7	19.5	ND
BMI	29.7 ± 5.8	29.7 ± 5	27.3 ± 5.1	27.5 ± 4.8	28.1 ± 4.4	ND
D.M. (%)	100	18.3	9.3	12.3	10.9	<0.05
HT (%)	96.4	100	90-7	82.7	35.2	<0.05
DL (%)	78.2	68.4	65.0	58.2	35.1	<0.05
Family history early CV (%)	7.0	9.2	8.2	7.3	11.1	ND
ACEIs/ARAII Treatment (%)	79.3	77.8	74.1	61.0	27.7	ND
Statin Treatment (%)	71.1	60.4	60.3	53.2	24.0	<0.05
Antiplatelet Treatment (%)	59.7	26.1	16.2	16.4	5.9	<0.05

Table 1: General and epidemiological parameters between groups according to the etiology of the CKD. p values show significant differences between some groups excluding healthy controls.

Etiology of Renal Disease	Stage of Renal Disease (% of patient)					eGFR (MDRD4)
	2	3	4	5	5 (% in Dialysis)	mL/min/1.73m²
Diabetic	0.8	35.9	31.9	31.4	22.4	31.5 ± 13.9
Vascular	2.9	56.3	20.7	20.1	14.6	38.1 ± 14.2
Systemic/Glom	2.2	27.0	28.9	41.9	33.0	30.8 ± 14.7
Others	1.9	34.7	22.0	41.5	32.1	33.4 ± 15.6
Controls	20.0	0.0	0.0	0.0	0.0	91.8 ± 16.7
						NS*

Table 2: Population distribution according to stage of CKD between different etiological causes of renal disease.
*No differences were found in the mean value of eGFR among the groups, excluding controls.

Etiology of Renal Disease	Diabetic	Vascular	Systemic/Glom	Others	Healthy Controls
Total Cholesterol (mg/dL)	170.9 ± 39.1	183.6 ± 39.4	179.4 ± 42.5	177.9 ± 38.3	203.3 ± 35.6
LDL Cholesterol (mg/dL)	95.0 ± 34.6	107.4 ± 34.4	101.5 ± 34.4	101.6 ± 32.1	127.3 ± 32.8
Triglyceride (mg/dL)	154.2 ± 95.1	144.1 ± 77.6	145.2 ± 82.2	140.9 ± 78.9	115.5 ± 67.5
Glycade Hemoglobin (%)	7.4 ± 1.4	5.8 ± 0.8	5.6 ± 0.8	5.6 ± 0.9	5.6 ± 1.0
Calcium (mg/dL)	9.2 ± 0.5	9.4 ± 0.5	9.2 ± 0.6	9.3 ± 0.6	9.3 ± 0.4
Phosphorus (mg/dL)	4.2 ± 1.0	3.7 ± 0.9	4.2 ± 1.2	4.0 ± 1.0	3.5 ± 0.5
Ca x P	38.8 ± 9.0	35.0 ± 9.3	39.4 ± 11.4	37.6 ± 10.1	33.0 ± 5.7
I-PTH (pg/mL)	167.5 ± 136.5	152.4 ± 177.1	180.6 ± 187. 7	192.85 ± 212.0	53.8 ± 14.5
Uric ac. (mg/dL)	6.6 ± 1.6	6.7 ± 1.6	6.8 ± 1.5	6.5 ± 1.5	5.0 ± 1.4
Hemoglobin (gr/dL)	12.5 ±1.6	13.4 ± 1.7	12.6 ± 1.6	12.7 ± 1.7	14.5 ± 1.4
Ferritin (ng/mL)	199.8 ± 201.7	219.9 ± 223.1	263.5 ± 381.2	240.0 ± 321.8	113.7 ± 116.6
Urine Mau/Cr (g/L)	685.6 ± 1171.4	300.7 ± 590.3	654.5 ± 996.2	369.8 ± 891.2	35.7 ± 47.6

Table 3: Laboratory parameters between groups according to the etiology of the CKD.

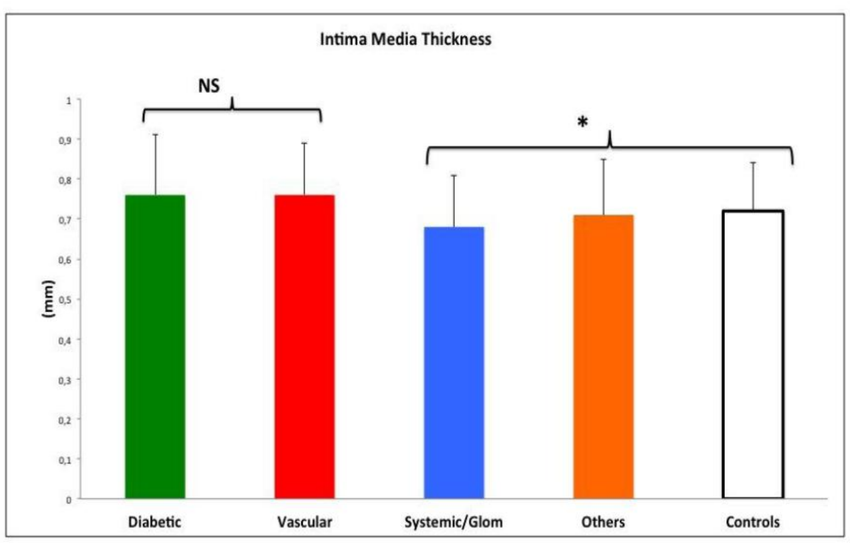

Figure 1.

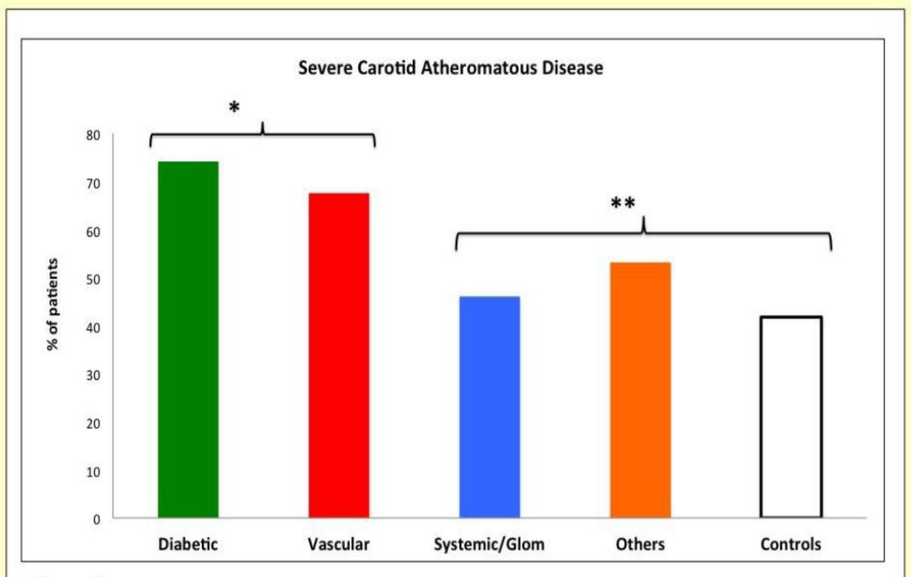

Figure 2.

Figure 1: In the bivariate analysis the IMT showed no differences between patients with DN vs VN, but both groups showed significantly higher IMT comparing with the other CKD etiologies and controls.
* p<0.05

Figure 2 : In the bivariate analysis the percentage of patients with severe carotid atheromatous disease was significantly higher in patients with DN vs VN (*p<0.05), and this was event more evident when compared with the others CKD etiologies and controls. (**p<0.001).

Risk of carotid severe atheromatous disease

	RR	IC 95%	
Etiology of CKD: Diabetic Nephropathy	**1.97**	**[1.3-2.9]**	**p<0.001**
Age (risk / year)	1.09	[1.0-1.1]	p<0.001
Gender (Male)	1.49	[1.2-1.8]	p<0.001
Smoking habit	2.12	[1.6-2.7]	p<0.001
Ex-Smoking habit	1.61	[1.2-2.0]	p<0.001
Stage V of CKD	2.20	[1.6-2.9]	p<0.001
Cholesterol (risk /mgr)	1.004	[1.001-1.007]	P=0.005

Table 4: After adjustment, the multivariate logistic regression proportional risk assessment, showed a significant higher risk of sever AD when DN was the etiology of CKD as compared with the others causes of CKD and controls. Others parameters related to high risk of severe AD are shown.

	RR	IC 95%	
Hypertension	1.32	[0.9-1.8]	P=0.07
Diabetes	1.33	[0.9-1.8]	P=0.07
PTH	1.0	[1.0-1.0]	P=0.1
CaxP	1.0	[0.9-1.0]	P=0.3
BMI	1.06	[0.9-1.0]	P=0.06
Triglyceride	1.0	[0.9-1.0]	P=0.6
ACEI/ARA II	0.9	[0.7-1.1]	P=0.5
Statine	1.1	[0.9-1.4]	P=0.1
Antiplatelet	1.2	[0.9-1.1]	P=0.1

Table 5: Shows the parameters that did not reach statistical significance after adjustment

CONCLUSIONS

In CKD patients without any CV event in the background clinical history, DN confers a two-fold higher adjusted risk of severe silent AD as compared with patients with CKD secondary to other etiologies.

Furthermore, this difference was independent of other conventional risk factors for atherosclerosis and CV events.

1: M Junyent et al. Nefrologia 2010:30(1):119-2