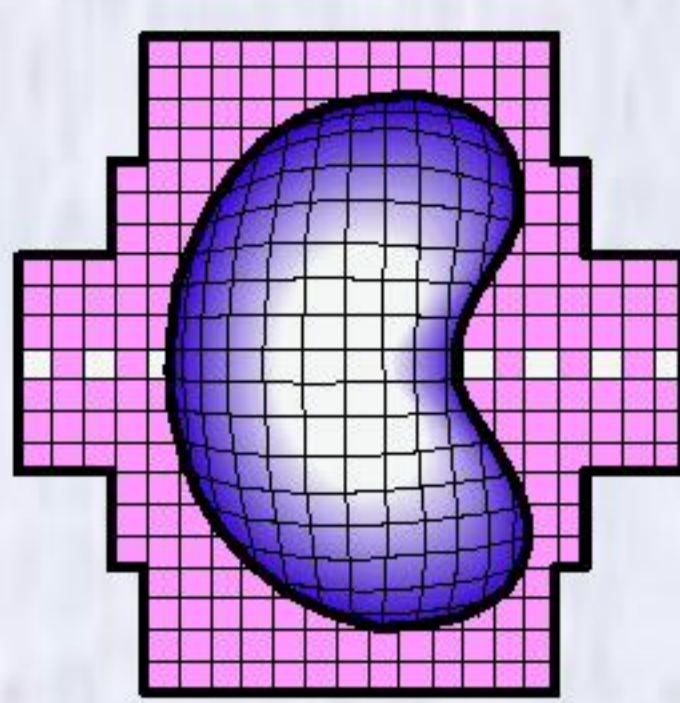


TRADITIONAL AND NOVEL CARDIOVASCULAR RISK FACTORS AS PREDICTORS OF ATHEROSCLEROSIS IN NON-DIALYSIS CHRONIC KIDNEY DISEASE

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BACKGROUND AND AIM

Although cardiovascular (CV) diseases are the leading cause of mortality in chronic kidney disease (CKD) and account for 10-fold higher death rate than in general population¹, the different contribution of traditional and uremia-related (non-traditional) CV risk factors is still a matter of debate².

Thus, we explored the relationships between certain markers of atherosclerosis and various CV risk factors in adults with or without CKD.

SUBJECTS AND METHODS

STUDY DESIGN: Cross-sectional, prospective enrollment over 6 Mo, single-center.

STUDY PARAMETERS:

I. Markers of atherosclerosis

- Carotid intima-media thickness (IMT - ultrasonography);
- Abdominal aortic calcification score (ACS - on plain lateral lumbar X-ray)³;
- Ankle-brachial index (ABI - VaSera® automatic waveform analyzer).

II. CV risk factors

- Traditional – gender, age, smoking, obesity, arterial hypertension, diabetes mellitus, serum cholesterol and triglycerides;
- Non-traditional – serum calcium (Ca), phosphate (PO₄), 25 hydroxy-vitamin D (25OHD), intact parathyroid hormone (iPTH), C-reactive protein (CRP), urinary albumin/creatinine ratio (ACR), and serum albumin.

STATISTICAL ANALYSIS:

For descriptive analysis percentages or median with 95%CI were used. Results were compared with Chi² or Mann-Whitney tests, as appropriate. Associations were tested by univariate (Spearman) and multiple linear regression (EXCEL, SPSS) analyses. Statistical significance was asserted when $p < 0.05$.

SUBJECTS:

- One hundred six patients with non-dialysis CKD: 58% >60 year-old; 9% stage 2, 47% - stage 3, 29% - stage 4, 15% - stage 5, 42% vascular nephropathies, CKD vintage 4 (95%CI 3,8 to 5,4%) years;
- Twenty-nine age- and gender-matched patients without CKD (45% >60 year-old).

SUBJECTS' CHARACTERISTICS AND STUDY PARAMETERS

Parameter	Non-CKD (n=29)	CKD (n=106)	p
Age (years) ^a	59 (48 to 67)	62 (47 to 73)	0.19
Males (%)	45	61	0.11
Active smokers (%)	17	11	0.59
Diabetes mellitus (%)	20	23	0.82
Arterial hypertension (%)	52	80	0.001
Overweight (BMI ≥26kg/m ²) (%)	35	40	0.61
eGFR (ml/min) ^a	72 (66 to 78)	31 (18 to 42)	<0.001
Aortic calcification score ^a	0 (0.2 to 1.6)	1.0 (2.3 to 4.1)	0.008
Aortic calcification score >1 (%)	24	54	0.006
Ankle-brachial index ^a	1.0 (1.0 to 1.1)	1.1 (1.0 to 1.1)	0.89
Carotid intima-media thickness ^a	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.26
Serum total cholesterol (mg/dl) ^a	186 (184 to 217)	183 (181 to 199)	0.24
Serum triglycerides (mg/dl) ^a	117 (107 to 159)	155 (145 to 173)	0.06
Urinary albumin/creatinine (mg/g) ^a	8.3 (6.1 to 11.1)	155 (522 to 1047)	<0.001
Serum iPTH (pg/ml) ^a	60 (51 to 67)	101 (134 to 199)	<0.001
Serum 25OHD (ng/ml) ^a	15.9 (13.6 to 21.3)	13.1 (13.1 to 15.7)	0.22
Serum phosphate (mg/dl) ^a	3.2 (3.1 to 3.5)	3.7 (3.6 to 4.0)	0.007
Serum total calcium (mg/dl) ^a	9.6 (9.4 to 9.8)	9.6 (9.4 to 9.7)	0.95
Serum C-reactive protein (mg/l) ^a	2.0 (2.1 to 5.0)	4.0 (5.3 to 9.2)	0.02
Serum albumin (g/dl) ^a	4.6 (4.5 to 4.7)	4.4 (4.3 to 4.5)	0.01

^a Median (95% CI) or percentage

RESULTS

Elevated PO₄, iPTH, CRP and ACR, lower albumin, but similar levels of serum lipids, calcium and calcidiol were found in CKD group as compared to Controls. High prevalence of vitamin D deficiency (<30ng/ml) was found irrespective of the kidney function (86% and 94% in non-CKD and CKD groups, respectively, $p=0.28$).

Despite various correlations observed in Spearman rank analysis, multiple linear regression models (log-transformed variables) retained fewer contributors to each of the studied atherosclerosis marker.

For example, age, PO₄, Ca and CKD vintage predicted ABI in a model that accounts for 17% of its variation.

Determinants of the ankle-brachial index

Variable	B	95% CI	p
Constant	1.52	1.13 to 1.91	<0.001
Log(Age)	-0.04	-0.08 to -0.008	0.02
Log(PO ₄)	-0.02	-0.15 to -0.04	0.001
Log(Ca)	-0.22	-0.37 to -0.07	0.004
Log(CKD vintage)	0.02	0.004 to 0.03	0.01

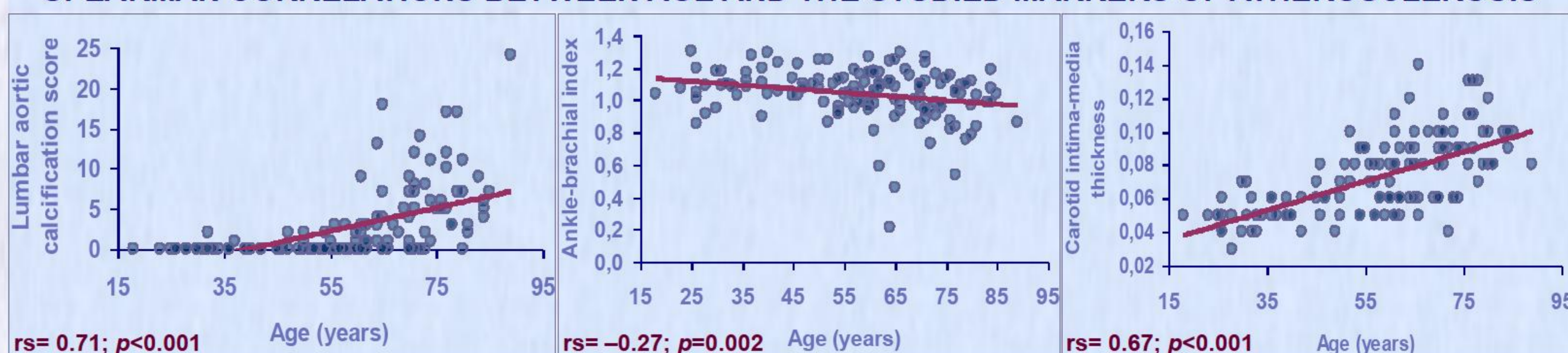
Adjusted R² = 0.17 $p < 0.001$

Dependent variable: Log(ABI)

Variables entered in step 1: Log(Age), Log(BMI), Log(eGFR), Log(uAlb/Cr), Log(Chol), Log(sAlb), Log(CRP), Log(PO₄), Log(tCa), Log(25OHD), Log(iPTH), Log(CKD vintage)

Older age, higher phosphatemia and calcemia were associated with lower ABI (which indicates peripheral atherosclerotic disease), while longer exposure to decreased GFR-related abnormalities was associated with higher ABI (marker of arterial stiffness).

SPEARMAN CORRELATIONS BETWEEN AGE AND THE STUDIED MARKERS OF ATHEROSCLEROSIS



Determinants of the aortic calcification score

Variable	B	95% CI	p
Constant	-6.70	-8.40 to -5.01	<0.001
Log(Age)	1.66	1.27 to 2.04	<0.001
Log(PO ₄)	0.66	0.12 to 1.21	0.02

Adjusted R² = 0.36 $p < 0.001$

Dependent variable: Log(ACS)

Variables entered in step 1: Log(Age), Log(eGFR), Log(CRP), Log(PO₄), Log(tCa), Log(25OHD), Log(iPTH), Log(CKD vintage)

In a model that accounts for 36% of ACS variation, only age and PO₄ were independently associated with aortic calcifications.

Determinants of the carotid intima-media thickness

Variable	B	95% CI	p
Constant	-5.07	-5.55 to -4.58	<0.001
Log(Age)	0.60	0.48 to 0.72	<0.001

Adjusted R² = 0.42 $p < 0.001$

Dependent variable: Log(IMT)

Variables entered in step 1: Log(Age), Log(eGFR), Log(CRP), Log(Chol), Log(PO₄), Log(tCa), Log(25OHD), Log(iPTH), Log(CKD vintage)

Similarly, age was the only determinant of carotid wall remodeling in a model that explained 42% of IMT variation.

CONCLUSIONS

Older age is the most constant predictor of atherosclerosis in non-dialysis CKD patients. Hyperphosphatemia seems to be involved in the risk for both arterial calcifications development and peripheral vascular disease, while hypercalcemia was another risk factor for peripheral atherosclerosis.

Serum lipid status, inflammation, parathyroid hormone and vitamin D seem to exert lesser influence on atherosclerosis, at least in an aged CKD population with high prevalence of hypovitaminose D.

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