

# The effect of vitamin K2 substitution on atherosclerosis and vascular calcification markers in non-dialyzed patients in chronic kidney disease stage 3-5

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## Objectives:

Vascular calcification and accelerated atherosclerosis are highly prevalent in patients with chronic kidney disease (CKD) and both have been associated with increased cardiovascular events. Although vitamin K2 may be protective against vascular calcification the role of vitamin D in promoting atherosclerosis and vascular calcification remains much more controversial and depending mostly on dose

**Aim of the study** was to assess the effect of substitution of vitamin K2 with small dose of vit D3 compared to vit D3 alone on development atherosclerosis, coronary artery calcification and serum calcification markers in 3-5. stage CKD non-dialyzed patients

## Methods:

75 consecutive CKD patients

Screening

42 patients with CACS ≥ 10

Randomization

Supplementation for 270 12 days

90 µg menaquinone (vitamin K<sub>2</sub>) + 10 µg cholecalciferol (vitamin D<sub>3</sub>) (group K+D; n=29)

10 µg cholecalciferol (vitamin D<sub>3</sub>) (group D; n=13)

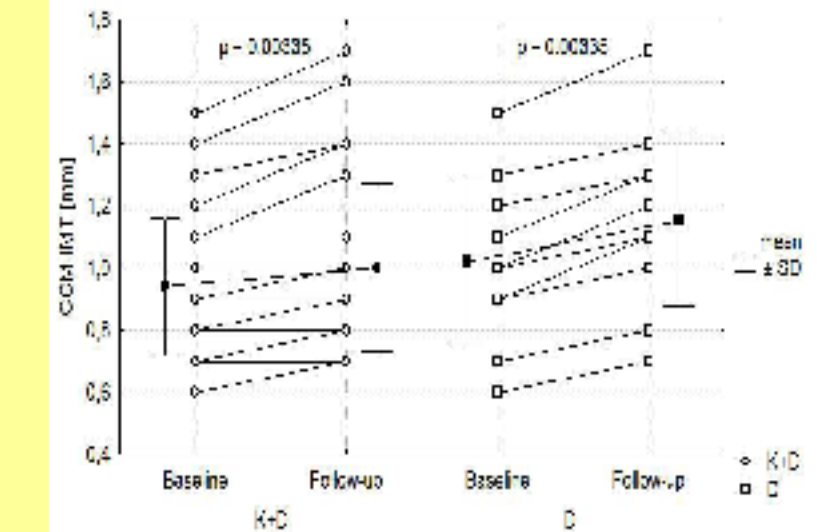
Study population

Age (Years)	F (n=18)		M (n=24)	
	56	1,5	60	3,0
(eGFR ml/min/m <sup>2</sup> )	24,8		11,2	
BMI	28,6		4,9	
Cause of CKD	Glomerulonephritis		15	
	Diabetes mellitus		8	
	Polycystic kidney diseases		4	
	Hypertension nephropathy		5	
	Tubulointestinal nephropathy		3	
	Unknown		5	

Before and after 270 12 days of treatment were measured:  
 - coronary artery calcification (CACS)  
 - common carotid intima media thickness (CCA-IMT)  
 - lipids, serum mineral parameters  
 - calcification markers: matrix Gla-protein (MGP), osteocalcin (OC), osteopregerin (OPG), fetuin A, FGF-23

## Results:

CACS before and after treatment

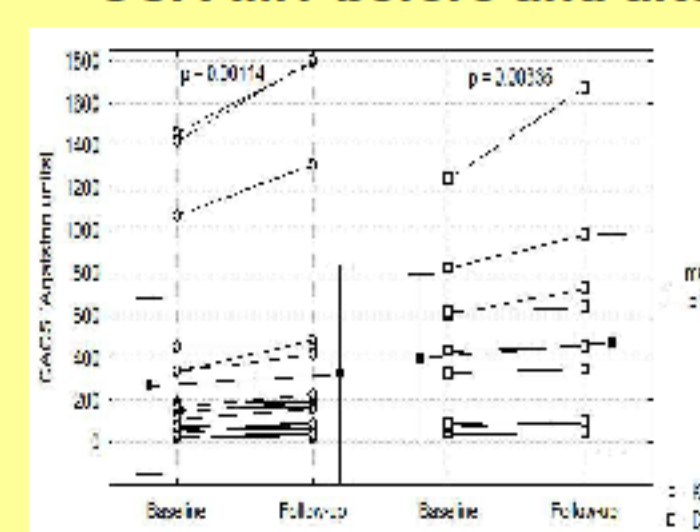


The change of CACS (K+D vs D group):  
 58.1 106.5 vs 74.4 127.1 A.u.ms  
 In patients with CACS <1000 A.u.:  
 18.2 29.1 vs 39.2 49.8, p=0.06

ΔCACS during treatment

CACS	Patient's number (n=40)	
	Vit K+D (n=28)	Vit D (n=12)
decrease	5 (5,4 5,2 A.u)	0
unchanged	2	0
increase	19	11

CCA-IMT before and after treatment

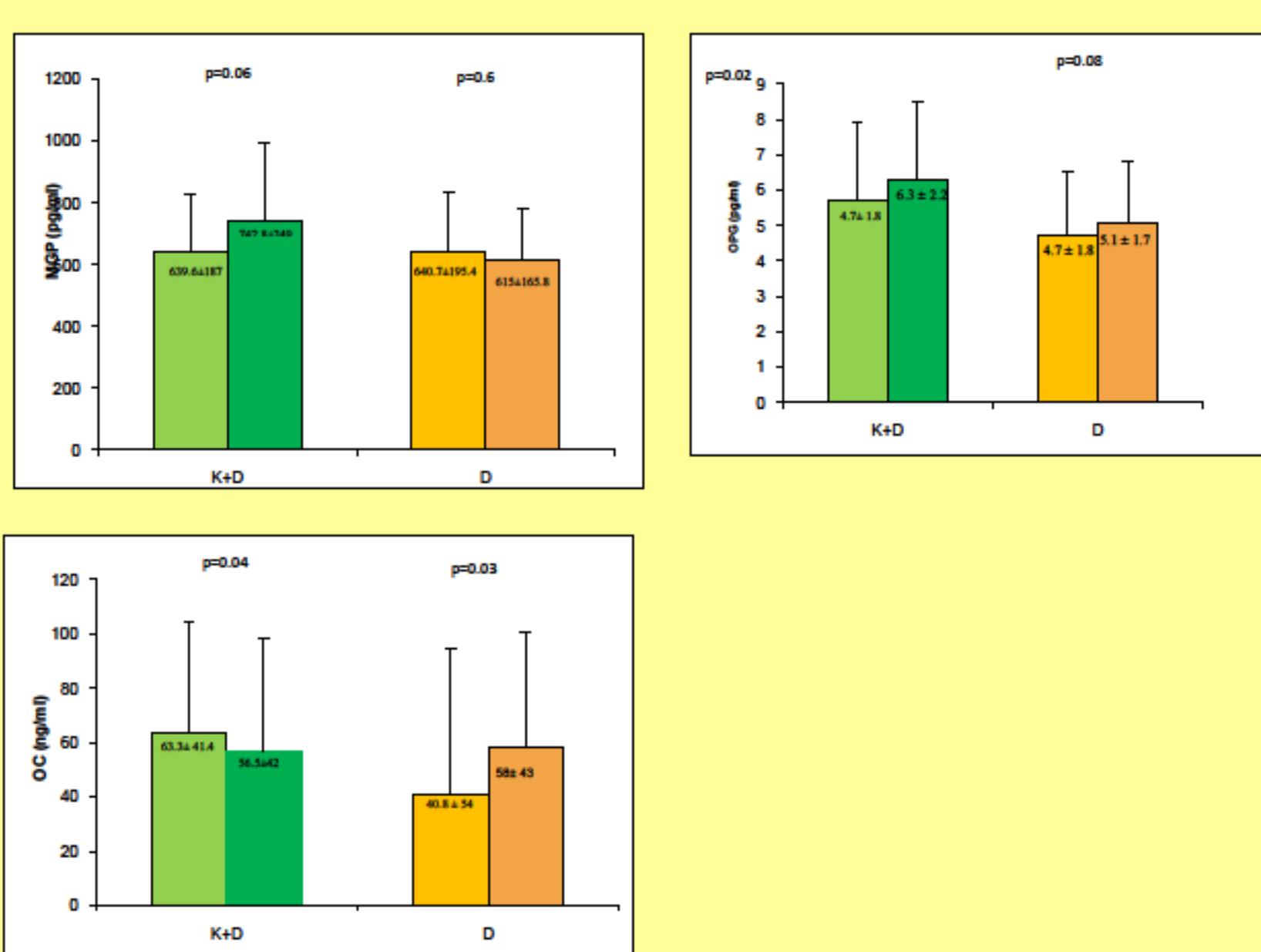


The change of CCA-IMT (K+D vs D group):  
 0.063 0.07 vs 0.14 0.05 mm, p<0.006;  
 6 vs 13.8%, p=0.02

Anthropometric and laboratory parameters

Parameter	Units	K+D (n=29)		p	D (n=13)		p
		Before treatment (n=29)	After treatment (n=28)		Before treatment (n=13)	After treatment (n=12)	
Age	years	59.4	6.0		55.4	15.2	0.36
BMI	kg/m <sup>2</sup>	30.3	4.6	0.92	28.7	5.2	no
Systolic pressure	mmHg	120	13	0.89	119	21	0.93
Diastolic pressure	mmHg	81	11	0.82	78	10	0.72
Creatinine	mg/dL	3.3	1.5	0.01	2.5	0.8	0.36
eGFR	ml/min/m <sup>2</sup>	22.2	9.8	0.08	30.3	12.7	0.71
Uric acid	mg/dL	6.8	1.4	0.16	6.5	1.9	0.2
Total cholesterol	mg/dL	208.5	66.7	0.56	167.5	106.8	0.06
Triglyceride	mg/dL	216.2	121	0.41	140	48.8	0.53
LDL	mg/dL	119.4	125.5	0.68	98.7	21.8	0.06
HDL	mg/dL	63.1	15.9	0.42	45.5	10	0.02
Glucose	mg/dL	113.8	19.2	0.3	107.1	12.5	0.05
Hemoglobin	g/L	11.8	1.4	0.25	13.2	1.8	0.02
Total protein	mg/dL	70.9	4.9	0.3	71.3	4	0.52
Albumin	mg/dL	40.8	3.5	0.96	42.4	1.9	0.94
Prothrombin time	seconds	132	0.4	0.86	131	0.5	0.96

The changes of calcification markers during vitamins treatment



Determinants affecting the changes of vascular damages

analyzed by stepwise multivariate linear regression analysis in patients treated with vitamin K2 and D

ΔCCA-IMT

Determinants	β	B	SEM	p
BMI	0.372758	0.150888	0.006110	0.002473
CACS baseline	0.537136	0.236919	0.000099	0.000044
FGF-23	0.671852	0.308345	0.000424	0.000195
OPG	-0.253463	0.14687	-0.00893	0.005175
Phosphate	-0.52148	0.308956	-0.09655	0.057203
CCA-IMT baseline	0.370088	0.256556	0.127682	0.088370

ΔCACS

Determinants	β	B	SEM	p
BMI	0.958959	0.059862	0.246	0.01439
CCA-IMT baseline	0.149027	0.054153	0.135	0.05061
OC	0.162953	0.063179	0.335	0.12976
BMI	0.106101	0.054868	2.426	1.25455
CxP	0.071632	0.059864	7.106	5.55193
hsCRP	0.058961	0.055999	1.255	1.23489

ΔCACS

Determinants	β	B	SEM	p
CACS baseline	0.537011	0.075161	0.174	0.02430
CRP	0.528678	0.080630	13.804	2.10526
CxP	0.200970	0.059652	43.264	12.8416

Serum mineral parameters

Parameter	Units	K+D (n=29)		p	D (n=13)		p
		Before treatment (n=29)	After treatment (n=28)		Before treatment (n=13)	After treatment (n=12)	
Calcium (Ca)	mg/dL	2.4	0.1	0.43	2.4	0.1	0.27
Phosphate (P)	mg/dL	1.4	0.4	0.09	1.1	0.2	0.004
Ca x P	mg <sup>2</sup> /dL <sup>2</sup>	3.3	1.0	0.09	2.7	0.6	0.002
PTH	pg/mL	194	145.1	0.33	134.0	76.5	0.5
25OH D3	ng/mL	20.8	9.8	0.004	24.8	12.9	0.01
FGF-23	pg/mL	41.3	120	0.96	16.7	15	0.86

## Conclusions:

- Vitamin K2 supplementation reduces the progression of intima media thickness in non-dialyzed subjects in CKD stage 3-5.
- The tendency to slow the progression of coronary artery calcification was noticed in patients treated with vitamin K2 particularly in those with less advanced vessel calcification at baseline.
- The mechanisms by which vitamin K2 exerts a protective role on the progression of vascular damage may be connected with its impact on MGP, OC and OPG secretion.

ClinicalTrials.gov Identifier: NCT01101698.

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