Effect of vitamin K2 supplementation on functional vitamin K deficiency in non-dialyzed patients with 3-5 stages of CKD: a randomized trial.

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OBJECTIVES

Recent data demonstrated a high prevalence of suboptimal levels of vitamin K and D in patients with CKD stage 3 to 5. Vitamin K is necessary for function of some extra-hepatic Gla-proteins in bone (osteocalcin-OC) and vessel wall matrix Gla protein (MGP). Both needs to undergo post-translational gammaglutamyl carboxylation to achieve full biologic activity. The carboxylation process is completely dependent on the availability of vitamin K which is a cofactor of this process. MGP is a powerfull inhibitor of vascular calcifiacation.

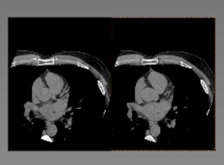
This prospective randomized intervention study assessed the impact of vitamin K2 supplementation on levels of the inactive form of MGP desphospho-uncarboxylated MGP (dp-ucMGP) in non-dialyzed 3 -5 stages CKD patients. Recent data demonstrated a high prevalence of suboptimal levels of vitamin K and D in patients with CKD stage 3 to 5.

METHODS

75 consecutive CKD patients

Screening

42 patients with CACS ≥ 10



Randomization

Supplementation for 270 12 days

90 µg menaquinone (vitamin K_2) + 10 µg cholecalciferol (vitamin D_3) (group K+D; n=29)

10 µg cholecalciferol (vitamin D_3) (group D; n=13)

Study population

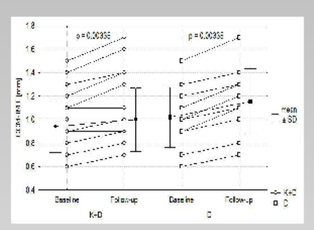
Age (Years)	F (*n=18*) 56 1,5	M (*n=24*) 60 3,0
(eGFR ml/min/m²)	24,8 11,2	
BMI	28,6 4,9	
Cause of CKD	Glomerulonephritis	15
	Diabetes mellitus	8
	Polycistic kidney diseases	4
	Hypertension nephropathy	5
	Tubulointestinal nephropathy	3
	Unknown	5

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), desphospho-uncarboxylated MGP (dp-ucMGP), osteocalcin (OC), osteopregerin (OPG), fetuin A, FGF-23

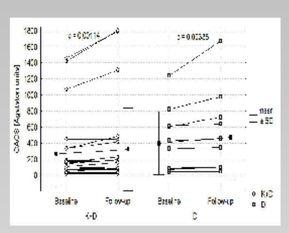
RESULTS

CACS before and after treatment



The change of CACS (K+D *vs* D group):
63.1±108.5 *vs* 74.4 127.1 A.u.,ns;
16% and 15.8%, p=0.91, respectively.

CCA-IMT before and after treatment

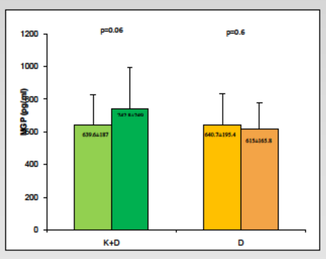


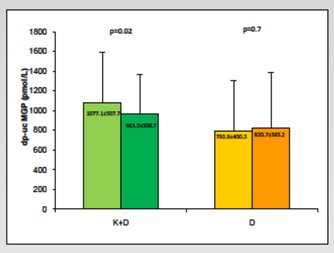
The change of CCA-IMT (K+D *vs* D group):
0.063 0.07 *vs* 0.14 0.05 mm, p<0.006;
6 vs 13.8%, p=0.02

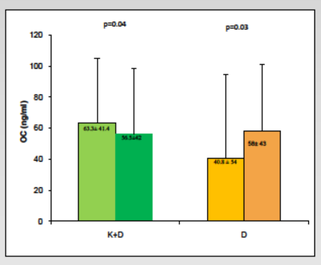
Anthropometric and laboratory parameters

Parametr	Jednostka	K+D (n= 29) Before treatment (n= 29)	K+D (n= 29) After traetment (n= 28)	K+D p	D (n=13) Before traetment (n=13)	D (n=13) After treatment (n=12)	D p
Age	years	59.4 9.6			55.4 15.2		0.36
BMI	kg/m²	30.3 4.6	29.8 4.1	0.92	28.7 5.2	28.5 4.9	ns
Systolic pressure	mmHg	129 13	131 12	0,85	119 21	121 19	0.93
Diastolic pressure	mmHg	81 11	79 12	0,82	78 10	81 9	0,72
Creatinine	mg/dL	3.3 1.5	4.3 2.7	0.01	2.5 0.8	2.6 0.9	0.36
eGFR	ml/min/m²	22.2 9.8	19.0 11.2	0.08	30.3 12.7	30.0 13.8	0.71
Uric acid	mg/dL	6.8 1.4	6.5 1.3	0.16	8.5 1.9	7.9 1.3	0.2
Total cholesterol	mg/dL	208.5 66.7	218.9 56	0.56	167.5 32.9	186.8 40.2	0.06
Triglyceride	mg/dL	215.2 121	198 113	0.41	140 48.8	149.8 52	0.53
LDL	mg/dL	119.4 49.5	125.5 47.3	0.65	96.7 21.8	108 33.1	0.06
HDL	mg/dL	53.1 15.9	57.2 28.1	0.42	45.8 10	51.3 12.2	0.02
Calcium (Ca)	mg/dL	2.4 0.1	2.4 0.2	0.43	2.4 0.1	2.5 0.2	0.27
Phosphate (P)	mg/dL	1.4 0.4	1.5 0.6	0.09	1.1 0.2	1.2 0.2	0.004
Ca x P	mg²/dL²	3.3 1.0	3.7 1.4	0.09	2.7 0.6	3.0 0.6	0.002
PTH	pg/mL	194 143.1	233 245.7	0.33	134.0 76.5	120.8 62.4	0.5
25OH D3	ng/mL	20.8 9.8	32.1 12.1	0.004	24.8 12.9	33.4 11.7	0.01

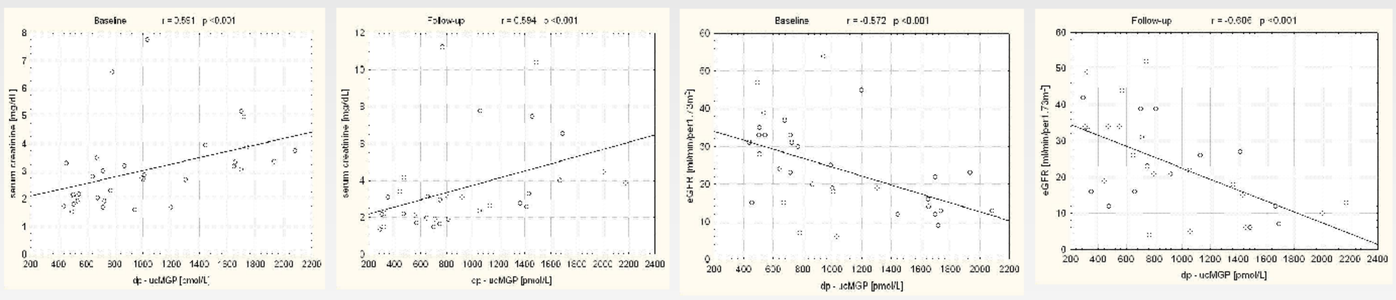
The changes of calcification markers during vitamins treatment



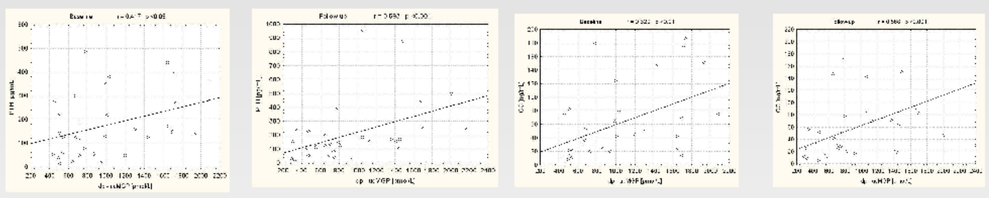




Correlation between desphospho-uncarboxylated (dp-ucMGP) level and kidney function



Correlation between dp-ucMGP level, PTH and osteocalcin (OC)



CONCLUSIONS

1. **The main determinant of dp-ucMGP level is the kidney function.**
2. **Circulating level of dp-ucMGP may be a marker of vascular vitamin K status in CKD patients.**
3. **The mechanisms by which vitamin K2 may exert the protective effect on progression of vessels damage are still uncertain, but may be connected with the impact of MK-7 on calcification's regulators, including the impact on the MGP carboxylation process.**

ClinicalTrials.gov Identifier: NCT01101698.

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