



VITAMIN K2 STATUS IN PATIENTS WITH PRE-DIALYSIS CHRONIC KIDNEY DISEASE

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ABSTRACT:

Vitamin K2 plays a key role in calcium homeostasis through activation of VKDP, including matrix Gla protein, a potent inhibitor of vascular calcification. Impaired vitamin K2 status results in increased circulating levels of inactive dephosphorylated uncarboxylated MGP (dp-ucMGP), which serves as a marker for vitamin K2 deficiency. CKD patients are at particularly high risk of vitamin K2 deficiency and its related complications.

Purpose: To assess vitamin K2 status indirectly by measuring plasma dp-ucMGP levels in patients with pre-dialysis CKD.

Material/Methods: This cross-sectional study included 71 adult Caucasian patients with pre-dialysis CKD stages G1–G4, classified according to KDIGO criteria. Participants were divided into three groups based on estimated glomerular filtration rate (eGFR). Serum creatinine, calcium, inorganic phosphate, and plasma dp-ucMGP levels were measured. Statistical analyses were performed using appropriate parametric and non-parametric tests.

Results: Significant differences were observed among the groups in age, renal function parameters, serum calcium, and phosphate levels ($p < 0.05$). Plasma dp-ucMGP concentrations did not differ significantly between CKD stages. However, when compared with recalculated reference values reported in the literature, dp-ucMGP levels in all groups were elevated, suggesting functional vitamin K2 deficiency. Sex-specific analysis revealed significantly higher dp-ucMGP levels in females with preserved to moderately reduced renal function, while no sex-related differences were observed in advanced CKD.

Conclusion:

Patients with pre-dialysis CKD demonstrated poor vitamin K2 status, as reflected by elevated dp-ucMGP levels. These findings support growing evidence that vitamin K2 deficiency is common and clinically relevant in the early stages of CKD.

Keywords: CKD, pre-dialysis patients, dephosphorylated uncarboxylated MGP, dp-ucMGP, vitamin K2

INTRODUCTION

K2 is a fat-soluble vitamin that is widely involved in calcium homeostasis. It is a cofactor for the enzyme gamma-glutamyl carboxylase and activates, through carboxylation, multiple extra hepatic vitamin K-dependent proteins (VDKP). Human matrix Gla protein (MGP) is an extracellular matrix VDKP that consists of 84 amino acids and, in its inactive form, contains 5 glutamic acid (Glu) residues. It is synthesized in bone and many other mesenchymal cells, and is also highly expressed by vascular smooth muscle cells and chondrocytes. These cell types position MGP to regulate locally calcium deposition, where ectopic calcification risks are very high [1]. That protein is widely recognized as one of the strongest natural inhibitors of vascular and soft tissue calcification, preventing calcium crystal formation and precipitation. The functionality of MGP depends on two post-translational modifications: phosphorylation and vitamin-K-dependent α -glutamate carboxylation [2]. The specific Glu-sites are carboxylated by vitamin K-dependent enzymes to form the functional Gla-residues with high affinity for calcium ions and hydroxyapatite. Into the extracellular space, active MGP regulates vascular homeostasis and calcium deposition.

Vitamin K2 is a vital nutrient newly recognized for supporting cardiovascular and bone health, shown in observational and intervention trials, in healthy and patient populations. Evidence confirms a widespread, “silent” deficiency of vitamin K2, driven by modern diets lacking fermented foods and poor conversion from K1. Studies indicate that ~30–50% of the population, particularly the elderly and those with chronic diseases, exhibit functional K2 insufficiency, which leads to silent, long-term vascular calcification and bone fragility [3].

In CKD, disease progression significantly increases the risk of cardiovascular disease and skeletal fragility, leading to heightened morbidity and mortality rates. Insufficient vitamin K2 is a significant factor in both the progression of CKD and the development of associated skeletal and cardiovascular complications [4].

Low vitamin K2 reduce carboxylation, resulting in elevated circulating levels of inactive dephospho-uncarboxylated MGP (dp-ucMGP). High dp-ucMGP serves as a marker for vitamin K2 deficiency, directly associated with increased vascular calcification, arterial stiffness, and cardiovascular mortality [5]. Clinical trials revealed that a reduction in active MGP predicts poor prognosis in patients due to cardiovascular complications [6]. Arterial calcification is a significant problem in patients with chronic kidney disease (CKD). It is a major factor in increased arterial stiffness, which contributes to the development of left ventricular hypertrophy, diastolic dysfunction, and heart failure.

Our study aimed to indirectly investigate vitamin K2 status in pre-dialysis CKD patients through plasma dp-ucMGP levels.

MATERIALS AND METHODS:

Study Population and Design:

Our study involved 71 adult Caucasian patients in pre-dialysis CKD stages (G1–G4), according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [7]. The stage of the disease was determined based on the estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease (MDRD) equation [8]. The study population were divided into three groups – Group 1 (normal or near-normal renal function) included patients with an eGFR \geq 90

ml/min/1.73 m² (stage G1), Group 2 (mild to moderately decreased renal function) included patients with a eGFR of 45-89 ml/min/1.73 m² (stages G2 and G3a), and Group 3 (moderately to severely decreased renal function) included patients with a eGFR of 15-44 ml/min/1.73 m² (stages G3b and G4). All participants have signed an informed consent. This research was conducted in accordance with the ethical principles for medical research as specified in the Declaration of Helsinki and received approval from the Research Ethics Committee of Medical University-Pleven.

Biochemical and Immunological Analyses:

Blood samples were collected in the morning after overnight fasting and were centrifuged at 2500 rpm for 10 min to separate the serum. The concentrations of serum creatinine (SCr), calcium (Ca), inorganic phosphate (Pi) were measured using the Roche Cobas E 311 analyzer. Human dephosphorylated uncarboxylated Matrix Gla Protein (dp-ucMGP) concentrations were measured using an enzymelinked immunosorbent assay kit (MyBioSource), according to the manufacturer’s instructions. Blood samples after centrifugation and plasma separation were frozen and stored at -20°C.

Statistical Analysis:

Statistical analyses were conducted using SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Data that followed a normal distribution were analyzed using One-way analysis of variance (ANOVA). For data that does not follow a normal distribution, the Kruskal-Wallis test was used for group comparisons, followed by the Mann-Whitney U test for pairwise comparisons. Statistical significance was considered at $p < 0.05$.

Table 1. Demographic and laboratory characteristics of the participants in the study groups.

Variables	Group 1 (n=16)	Group 2 (n=33)	Group 3 (n=22)	p-Value
Male/Female (n/n)	5/11	23/10	11/11	
Age (years) ¹	48.81±16.97	67.03±9.69	68.09±11.48	<0.001
eGFR(ml/min) ¹	102.31±11.75	60.94±11.61	25.82±9.71	<0.001
SCr(μmol/l) ¹	68.75±13.92	109.76±22.78	236.64±87.47	<0.001
Ca (mmol/l) ¹	2.42±0.11	2.39±0.09	2.32±0.15	0.029
Pi (mmol/l) ¹	1.11±0.15	1.15±0.20	1.28±0.27	0.041
Dp-ucMGP (ng/ml) ²	8.20(7.35-10.38)	8.14(7.41-9.03)	7.82(7.15-10.78)	0.62

¹mean ± SD; ²median and IQR. Abbreviations: eGFR, estimating glomerular filtration rate; SCr, serum creatinine; UA; Ca, calcium; Pi, inorganic phosphate; Dp-uc-MGP, dephosphorylated uncarboxylated Matrix Gla Protein. $p < 0.05$, statistically significant.

RESULTS:

The mean age of the participants, the concentrations of Ca, inorganic phosphate (Pi), SCr, GFR and Dp-ucMGP of the studied groups are presented in Table 1:

There is no currently widely accepted reference range for plasma dp-ucMGP expressed in ng/mL in the literature. In clinical studies assessing vitamin K status, reference intervals for dp-ucMGP have been established in Caucasian populations using the chemiluminescent immunoassay IDS®-iSYS Ina Ktif (dp-ucMGP) assay [9]. However, different ELISA kits and automated assay platforms may produce varying absolute concentrations, which limits direct standardization across laboratories. Based on the reported reference range for healthy adults of 300–532 pmol/L and a molecular weight of dp-ucMGP of 11 kDa (11,000 g/mol), this corresponds to an estimated concentration of approximately 3.3–5.9 ng/mL. These converted values, however, have not yet been formally established or accepted as reference ranges.

The sex distribution was comparable across groups, with no apparent imbalance between males and females. The three groups differed significantly in age, with participants in Group 1 being significantly younger than those in Groups 2 and 3 ($p < 0.001$). Markers of renal function differed significantly across the three groups. A progressive decline in estimated glomerular filtration rate (eGFR) from Group 1 to Group 3 was observed, accompanied by a corresponding increase in serum creatinine levels ($p < 0.001$ for both parameters). Serum calcium and inorganic phosphate levels also showed statistically significant differences among the groups. Calcium concentrations were lower in Group 3 compared with Groups 1 and 2 ($p = 0.029$), while phosphate levels were higher in Group 3 ($p = 0.041$). Plasma dp-ucMGP concentrations, expressed as median and interquartile range, did not differ significantly among the three groups ($p = 0.620$).

Overall, these findings demonstrate clear group-related differences in age, renal function, and mineral metabolism, while dp-ucMGP levels remained comparable despite advancing renal impairment.

Mean concentrations of plasma dp-ucMGP in ng/ml are shown in Fig. 1. If we accept the recalculated values in ng/ml, we can conclude that the subjects studied have a functional vitamin K2 deficiency. Levels of dp-ucMGP varied according to renal function. The highest mean dp-ucMGP values were observed in participants with eGFR >90 mL/min, whereas lower levels were detected in patients with moderately reduced renal function (eGFR 45–89 mL/min). The differences between groups were not statistically significant ($p > 0.05$).

Fig. 1. Plasma dp-ucMGP levels according to estimated glomerular filtration rate (eGFR).

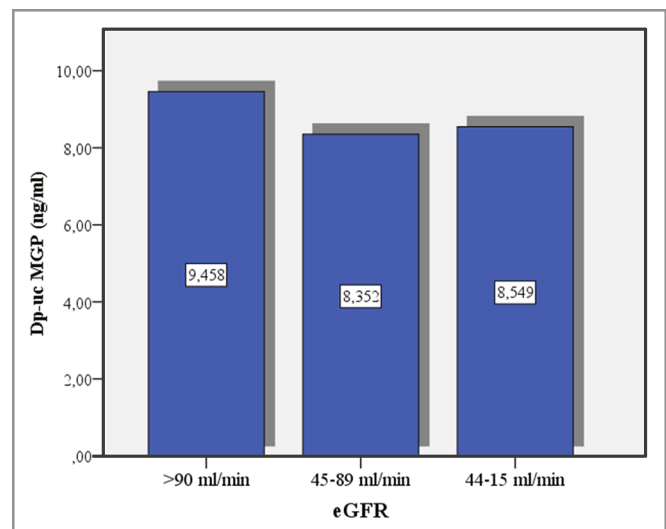
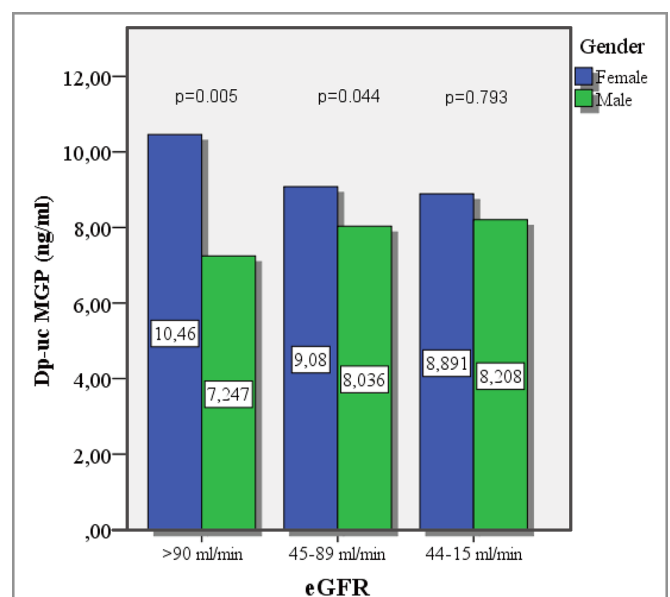


Figure 2 presents dp-ucMGP concentrations (ng/ml) in females and males stratified by renal function. In Group 1, females had significantly higher dp-ucMGP levels than males ($p = 0.005$). A statistically significant gender difference was also observed in Group 2 ($p = 0.044$), with higher dp-ucMGP levels in females. In contrast, no significant difference between sexes was detected in Group 3 ($p = 0.793$). These findings indicate that sex-related differences in dp-ucMGP are evident in patients with preserved to moderately reduced renal function but are attenuated in advanced renal impairment.

Fig. 2. Sex-specific differences in dephosphorylated uncarboxylated matrix Gla protein (dp-ucMGP) levels across estimated glomerular filtration rate (eGFR) categories.



DISCUSSION:

In CKD patients, vascular calcification occurs more rapidly and at earlier stages, serving as an independent risk factor for increased morbidity and mortality [10]. In recent years, the understanding of the pathogenetic mechanisms leading to accelerated arterial calcification in CKD has changed significantly. Early models treated calcification as a non-biological endpoint of mineral imbalance in extracellular fluid. Recent research has shifted the view of vascular calcification in CKD from a passive precipitation of calcium-phosphate due to hyperphosphatemia and hypercalcemia toward an actively regulated, cell-driven process. This modern understanding highlights the central role of vascular smooth muscle cells (VSMCs), which transdifferentiate into osteoblast-like cells. These processes are influenced by uremic toxins, inflammation, and, most importantly, the lack of adequate amounts of calcification inhibitors such as MGP [11].

MGP requires vitamin K-dependent carboxylation to inhibit vascular calcification, and its inactive form dp-ucMGP reflects functional vitamin K2 deficiency. Elevated dp-ucMGP levels are associated with increased vascular calcification in CKD patients [12]. Global evidence indicates that CKD patients are characterized by poor vitamin K status [13]. Our results demonstrate elevated levels of dp-ucMGP, respectively, poor vitamin K2 status in the group of patients we studied. Multiple factors can affect vitamin K stores in CKD. Some of them are related to dietary inadequacy and absorption issues in the general population. Others can be explained by several interrelated renal-specific factors:

- Dietary restrictions due to the high potassium (such as green leafy vegetables) and phosphate content (such as dairy products). Both food groups are important sources of vitamins K1 and K2 [14].

- Uraemia-associated dysbiosis in more advanced stages decreases the population of bacteria that synthesize vitamin K2 and further impairs the bioavailability of the vitamin [15].

- Decreased activity of enzymes of the vitamin K cycle: Experimental studies in uremic rodent models and human CKD tissues demonstrate reduced activity of γ -glutamyl carboxylase, impairing vitamin K-dependent carboxylation and recycling within the vitamin K cycle [4].

- Drugs: Anticoagulant warfarin, phosphate binders like sevelamer, proton pump inhibitors, and certain antibiotics can indeed deplete vitamin K2 levels by interfering with its absorption, metabolism, or gut microbiota production [4].

- Increased need for calcification inhibitors: Increased vascular calcification heightens the body's demand for VKDP, like active MGP, accelerating vitamin K2 consumption and depletion during the carboxylation process [16].

- Malabsorption and altered transport: Uremia impairs the absorption and transport of fat-soluble vitamins like vitamin K2 in CKD patients due to disrupted lipid metabolism and HDL dysfunction [17].

Available evidence suggests that sex-related differences in circulating dp-ucMGP concentrations may exist, with several studies reporting significantly higher levels in women compared with men in both healthy populations and selected clinical cohorts [9]. However, these findings are not entirely consistent across studies and are often derived from relatively small or disease-specific populations. Our results are consistent with these findings. Sex-related differences in dp-ucMGP levels in patients with preserved and moderately reduced renal function may reflect gender-specific regulation of vascular calcification processes. Matrix Gla protein is a key inhibitor of vascular calcification, and circulating dp-ucMGP represents its inactive form, which is closely associated with vitamin K deficiency and increased calcification risk. Higher dp-ucMGP levels in women in Groups 1 and 2 may therefore indicate sex-dependent differences in vascular biology, hormonal regulation, or vitamin K-dependent MGP activation. In advanced CKD (Group 3), profound disturbances of mineral and bone metabolism, including hyperphosphatemia and altered calcium handling, may dominate MGP regulation and vascular calcification pathways, thereby attenuating sex-related differences in dp-ucMGP levels (Fig.2). Consequently, while sex appears to be a relevant covariate in the interpretation of dp-ucMGP measurements, further large-scale, population-based studies are required to confirm these observations and to clarify their biological and clinical significance.

CONCLUSION:

The patients with chronic kidney disease included in this study exhibited poor vitamin K2 status. The data obtained are concerning and are consistent with findings from some recent studies and reviews, which indicate that poor vitamin K2 status is highly prevalent and clinically significant in patients in pre-dialysis stages of CKD.

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