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Research Article

The relationship between undercarboxylated matrix Gla protein and cardiovascular diseases in pre-dialysis chronic kidney disease patients

Borislav Ignatov[1], Tatyana Simeonova[1], Tsvetelina Eftimova[2], Anelia Dimitrova[1], Krasimir Kostov[1]

1 *Department of Physiology and Pathophysiology, Medical University – Pleven, Pleven, Bulgaria*
2 *Hemodialysis Unit, St. Marina Hospital, Pleven, Bulgaria*
Corresponding author: Borislav Ignatov (dr_bignatov@abv.bg)

Summary

Introduction: Chronic kidney disease (CKD) patients are at high risk for cardiovascular disease, largely due to the presence of vascular calcification and its associated complications. Undercarboxylated matrix Gla protein (ucMGP), which inhibits vascular calcification, plays a crucial role in preventing this condition.

Aim: Our study aimed to compare ucMGP levels in CKD patients with preserved and reduced renal function and to evaluate its role as a biomarker for cardiovascular risk.

Materials and methods: We studied 84 patients with predialysis CKD. They were divided into two groups according to the kidney function: Group I – patients with preserved renal function (GFR ≥ 90 ml/min) and Group II – patients with mild to severely decreased renal function (GFR between 15 and 89 ml/min). Blood samples were analyzed using the Cobas E 311 automated analyzer and the ucMGP levels were measured using an ELISA kit from Abbexa, UK.

Results: In Group I, CVD patients had significantly higher inorganic phosphates, blood urea nitrogen and serum creatinine. In Group II, CVD patients had significantly higher ucMGP concentrations. UcMGP levels were associated with age and CVD in Group II and highly correlated with inorganic phosphate and serum creatinine levels in Group I.

Conclusions: UcMGP levels show a significant increase in CKD patients with CVD and are strongly connected to various renal function indices, indicating its potential as a biomarker for cardiovascular risk assessment.

Key words: Cardiovascular risk, chronic kidney disease, undercarboxylated matrix Gla protein, vascular calcification

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Introduction

Patients with chronic kidney disease (CKD) exhibit an elevated cardiovascular risk manifesting as coronary artery disease, arrhythmias, heart failure, and sudden cardiac death. The incidence and prevalence of cardiovascular events is already significantly higher in patients with early CKD stages compared with the general population (Yuan et al. 2017; Jankowski et al. 2021).

Vascular calcification has emerged as a critical aspect of CKD, with implications for cardiovascular morbidity and mortality. The complex pathophysiology of vascular calcification, involving various factors such as Matrix Gla protein, fetuin-A, and calciprotein particles, highlights the need for a multifaceted comprehensive approach to reduce and prevent these complications (Izzo et al. 2024).

The discovery of vitamin K2-dependent matrix Gla-protein (MGP) as a local tissue inhibitor of vascular calcification has diametrically changed the mechanistic understanding of this process and given way to new search for biomarkers in CVD (Galunska et al. 2024). Studies on MGP knockout mice have shown that they develop severe aortic calcification and often experience aortic rupture leading to death at around 6 weeks old (Luo et al. 1997). Human Keutel syndrome, which results from mutations in the MGP gene, also presents with vascular calcification (Cancela et al. 2021). MGP prevents calcium (Ca) crystal formation directly by working alongside other calcification inhibitors, and indirectly by influencing transcription factors that prevent vascular cells from differentiating into osteoblast-like cells (Jiang at al. 2021). The activation of MGP is dependent on post-translational carboxylation, which is a process that requires vitamin K2 (Wei et al. 2019).

Recent studies have demonstrated that lower serum levels of uncarboxylated MGP (ucMGP), the precursor to the active carboxylated MGP protein, are observed with end-stage renal disease (stage G5 of CKD) as compared to healthy controls (Parker et al. 2009). It is not known, however, whether persons with less severe to significant decrements in kidney function (stages G2–G4 of CKD) also have lower ucMGP levels compared to persons with preserved kidney function (stage G1 of CKD). For this purpose, we compared the serum levels of ucMGP in CKD patients with proven CVD who had preserved renal function (stage G1) with a group of patients who had mild to significant decreased renal function (stages G2–G4).

Materials and methods

Participants

We investigated 84 patients, aged between 31 and 87 years, comprising 32 men and 52 women, in predialysis CKD stages. All participants have signed an informed consent. The patients were divided into two groups based on the Kidney Disease: Improving Global Outcomes (KDIGO) recommendations, which define CKD in five stages (G1–G5), according to the kidney function and glomerular filtration rate (GFR) (National Kidney Foundation 2012): Group I (preserved renal function) – patients with GFR ≥ 90 ml/min/1.73 m^2 (stage G1) and Group II (mild to severely decreased renal function) – patients with GFR between 15–89 ml/min/1.73 m^2 (stages G2 – G4). Patients with CKD on hemodialysis, stage G5 (GFR < 15 ml/min/1.73 m^2), were excluded from the study. The GFR was calculated by MDRD eGFR calculator based on data of age, race, gender, and serum creatinine (SCr) concentration. The mean age of the patients, the concentrations of Ca, inorganic phosphate (Pi), blood urea nitrogen (BUN), SCr, GFR and ucMGP in the studied groups are presented in Table 1:

Table 1. Clinical characteristics of the groups.

Parameter	Group I n = 15	Group II n = 69	p-value
Age (years)	58.2 ± 15.5	66.13 ± 11.2	
Ca (mmol/l)	2.48 ± 0.10	2.5 ± 0.24	p = 0.806
Pi (mmol/l)	1.15 ± 0.15	1.16 ± 0.18	p = 0.902
BUN (mmol/l)	5.87 ± 1.32	8.80 ± 3.95	p = 0.002*
SCr (μmol/l)	62.8 ± 12.28	125.93 ± 51.63	p < 0.001*
GFR (ml/min)	102.87 ± 15.05	52.64 ± 20.99	p < 0.001*
ucMGP (ng/ml)	2.31 ± 1.13	2.29 ± 0.9	p = 0.888

Results are presented as mean ± SD. Ca – calcium, Pi – inorganic phosphate, BUN – blood urea nitrogen, SCr – serum creatinine, GFR – glomerular filtration rate, ucMGP – undercarboxylated MGP. A statistically significant difference, p < 0.05*.

Methods

Blood samples collecting: Blood samples were collected in the morning after overnight fasting. The biochemical tests for Ca, Pi, and SCr were conducted using the biochemical analyzer Cobas E 311 (Roche Diagnostics). The ucMGP concentrations were measured with the ELISA kit from Abbexa, UK (abx257511) in accordance with the manufacturer's instructions.

Statistical analysis: Statistical analyses were carried out using SPSS v23.0. Data were assessed for normality of distribution through the Kolmogorov-Smirnov and Shapiro-Wilk tests. The nonparametric Mann-Whitney test was used for group comparisons. Spearman's rank correlation was utilized to examine the relationship between variables. The strength of correlations was evaluated based on the correlation coefficient (r) on a 5-point scale: weak ($r < 0.3$), moderate ($0.3 < r < 0.5$), strong ($0.5 < r < 0.7$), very strong ($0.7 < r < 0.9$), and perfect ($0.9 < r < 1$). Values of $p < 0.05$ were considered statistically significant.

Patient data collection: Data about accompanying cardiovascular diseases – hypertension and coronary artery disease (CAD) were collected from medical documentation of the participants.

Results

Serum concentrations of Ca and Pi in group I and group II were within the reference range. The statistically significant differences found in BUN, SCr, and GFR concentrations between the groups were as expected. No significant difference was found in ucMGP concentrations between group I and group II (Table 1). In group I, males showed statistically significantly increased ucMGP and creatinine concentrations and decreased Pi concentrations compared to females. In group II, we also found statistically significantly higher ucMGP and creatinine concentrations in males compared to females (Table 2). Upon comparing group I with group II, it was found that there were no significant differences in ucMGP levels between males and females, respectively.

In group I, patients with CVD had statistically significantly higher concentrations of Pi, BUN and SCr compared to non-CVD patients. In group II, patients with CVD showed statistically significantly higher levels of Pi and SCr and lower GFR compared to those without CVD. The concentration of ucMGP in patients with CVD was higher than in patients without CVD, and the difference was statistically

Table 2. Concentrations of Ca, Pi, BUN, SCr, GFR and ucMGP in the male and female populations of the two study groups.

Parameter	Group I			Group II		
Gender	**Male n = 4**	**Female n = 11**	**p-value**	**Male n = 28**	**Female n = 41**	**p-value**
Ca (mmol/l)	2.54 ± 0.08	2.46 ± 0.11	p = 0.089	2.44 ± 0.1	2.53 ± 0.29	p = 0.131
Pi (mmol/l)	1.13 ± 0.15	1.19 ± 0.19	p = 0.005*	1.31 ± 0.14	1.1 ± 0.19	p = 0.054
BUN (mmol/l)	5.78 ± 0.65	5.91 ± 1.52	p = 0.948	9.05 ± 3.98	8.63 ± 3.98	p = 0.582
SCr (µmol/l)	74.0 ± 10.17	58.73 ± 10.56	p = 0.013*	149 ± 53.34	110.17 ± 44.55	p = 0.002*
GFR (ml/min)	103.25 ± 10.7	102.73 ± 16.8	p = 0.844	49.21 ± 18.73	54.98 ± 22.26	p = 0.346
ucMGP (ng/ml)	3.53 ± 0.4	1.87 ± 0.97	p = 0.006*	2.28 ± 0.85	2.09 ± 0.89	p = 0.017*

Results are presented as mean ± SD. Ca – calcium, Pi – inorganic phosphate, BUN – blood urea nitrogen, SCr – serum creatinine, GFR – glomerular filtration rate, ucMGP – undercarboxylated MGP. A statistically significant difference, p < 0.05*.

Table 3. Cardiovascular comorbidities and concentrations of Ca, Pi, BUN, SCr, GFR and ucMGP in the two study groups.

Parameter	Group I			Group II		
CVD (%)	**No (80%)**	**Yes (20%)**	**p-value**	**No (41.2%)**	**Yes (58.8%)**	**p-value**
Ca (mmol/l)	2.48 ± 0.12	2.5 ± 0.05	p = 0.784	2.53 ± 0.34	2.48 ± 0.11	p = 0.469
Pi (mmol/l)	1.11 ± 0.12	1.31 ± 0.17	p = 0.043*	1.15 ± 0.16	1.17 ± 0.18	p = 0.761
BUN (mmol/l)	7.18 ± 3.13	9.98 ± 4.1	p = 0.003*	5.85 ± 1.48	5.97 ± 0.38	p = 0.665
SCr (µmol/l)	59.92 ± 11.6	74.33 ± 8.02	p = 0.001*	107.72 ± 55.88	139.13 ± 44.51	p = 0.043*
GFR (ml/min)	102.7 ± 16.3	103.67 ± 11.6	p = 0.612	62.28 ± 21.8	45.65 ± 17.44	p = 0.002*
ucMGP (ng/ml)	2.07 ± 1.1	3.28 ± 0.79	p = 0.060	1.98 ± 0.73	2.52 ± 0.96	p = 0.009*

Results are presented as mean ± SD. CVD – cardiovascular disease, Ca – calcium, Pi – inorganic phosphate, BUN – blood urea nitrogen, SCr – serum creatinine, GFR – glomerular filtration rate, ucMGP – undercarboxylated MGP. A statistically significant difference, p < 0.05*.

significant. The summary data on cardiovascular diseases and the other studied parameters of the participants in the two studied groups are presented in Table 3:

In group I, we found strong positive correlations between ucMGP concentrations and Pi (r = 0.532, p = 0.041) (Fig. 1), and between ucMGP concentrations and SCr (r = 0.693, p = 0.004) (Fig. 2).The correlation analysis showed that in group II, there was a weak positive correlation between ucMGP concentrations and age (r = 0.265, p = 0.028) (Fig. 3), as well as a moderate positive correlation between ucMGP concentrations and CVD (r = 0.315, p = 0.008) (Fig. 4).

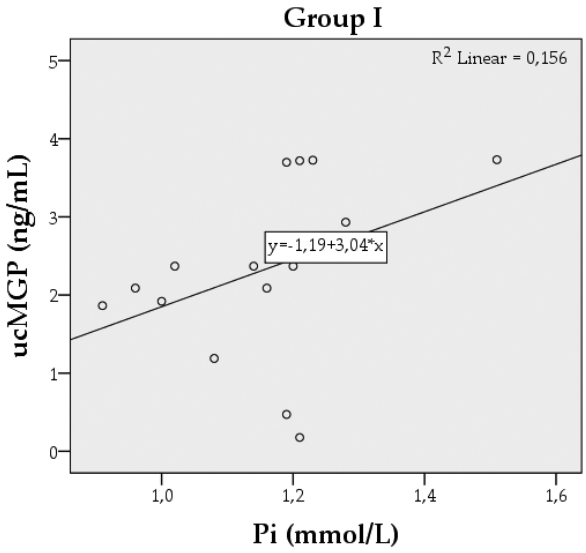

Figure 1. Positive correlation between ucMGP levels and serum Pi in group I.

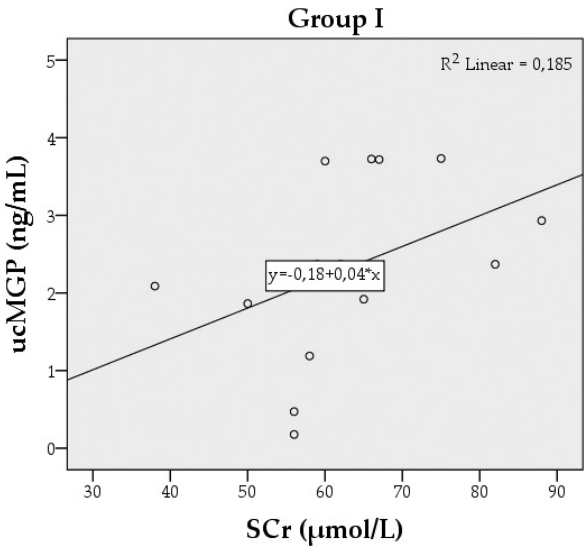

Figure 2. Positive correlation between ucMGP levels and SCr in group I.

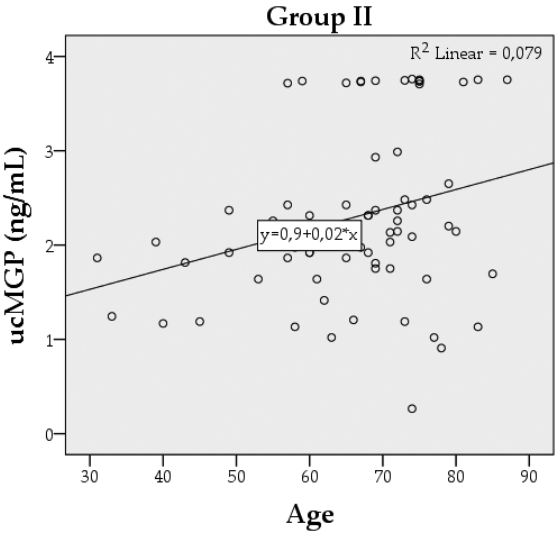

Figure 3. Positive correlation between the levels of ucMGP and age in group II.

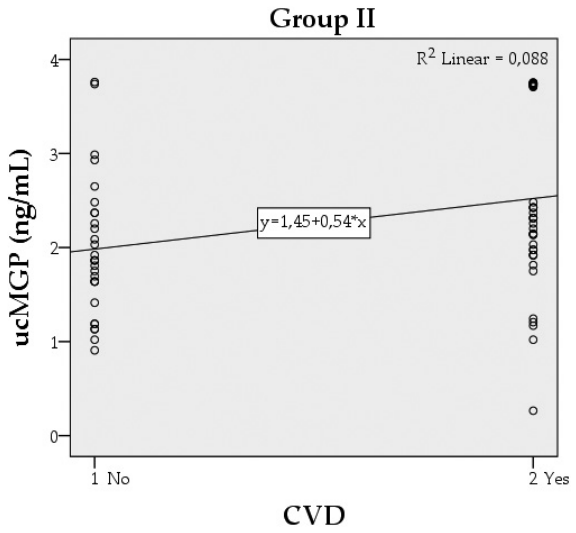

Figure 4. Positive correlation between the levels of ucMGP and CVD in group II.

Discussion

In patients with CKD, vascular calcification occurs more rapidly and earlier and is an independent risk factor for higher morbidity and mortality. CKD-specific risk factors contribute to the importance of vascular calcification and the severity of the particular vascular problems in this patient population. Abnormal mineral metabolism is partly responsible for vascular calcification (Garland et al. 2008). In vitro studies have shown that in the presence of hyperphosphatemia, vascular smooth muscle cells are transformed into osteoblast-like cells that can express proteins that regulate mineralization (Shanahan et al. 2011). High serum Pi concentrations are associated with high cardiovascular disease risk in both the general population and CKD patients (Lim et al. 2015). Hyperphosphatemia is a late finding in CKD. Serum Pi is maintained within normal limits until the GFR falls to less than 20 ml/min (Levin et al. 2007). There is evidence that Pi levels in the reference range are associated with an increased risk of cardiovascular events (Craver et al. 2007). Elevated serum Pi levels, even within the normal reference range, have been associated with vascular calcification and stiffness in patients with and without CKD (Kendrick and Chonchol 2011). Recent studies confirm that as kidney function declines, serum Pi levels rise and induce the development of hypertension, atherosclerosis, vascular calcification, cardiac valvular calcification, left ventricular hypertrophy, and myocardial fibrosis by distinct mechanisms (Zhou et al. 2021). Our results support this data. In group I, we found Pi concentrations within the reference range, but significantly higher in patients with CVD compared to patients without CVD (Table 3). Also, elevated levels of ucMGP in our study show a strong positive correlation with elevated levels of SCr and Pi, which may be related to vascular calcification and fibrosis (Figs 3, 4). The lack of inhibitors of vascular calcification and especially carboxylated MGP is the main reason for the deposition of Ca in the vascular wall and a decrease in its elasticity. It was considered that ucMGP is one of the most powerful inhibitors of vascular calcification found in humans (Roumeliotis et al. 2018). Our data do not show statistically significant differences in ucMGP levels in patients with preserved and reduced renal function (Table 1) but support to a large extent the relationship between ucMGP levels and cardiovascular disease. We found higher levels of ucMGP in patients with hypertension and CAD compared with those without CVD. In the group with reduced renal function the difference was statistically significant (Table 3). An interesting result was the positive correlation between ucMGP levels and CVD in the same group of patients, suggesting the involvement of ucMGP in the pathogenesis of vascular complications already in the early stages of the disease (Fig. 4). We also found a positive correlation of ucMGP with age and CVD (Fig. 3). Experimental observations suggest that local vascular but not systemically overexpressed MGP is protective against vascular calcification (Krueger et al. 2009). The accumulation of ucMGP within calcified vessel walls is a possible explanation for its low circulating level (Hermans et al. 2008). This thesis can largely explain the lack of statistical significance in ucMGP levels in relation to cardiovascular risk in group II of our study with the progression of renal failure. In both studied groups, men's levels of ucMGP were significantly higher than women's, which is probably related to a higher cardiovascular risk in the male population with CKD (Table 2). Similar results were reported by Malhotra et al.

(2022) in a study of the association of ucMGP levels with vascular calcification, arterial stiffness among 7066 community-dwelling adults. They found higher ucMGP levels associated with older age and male sex. In age- and sex-adjusted analyses, higher ucMGP concentrations were also associated with other cardiovascular risk factors including higher blood pressure, higher body mass index, hyperlipidemia, and lower estimated glomerular filtration rate.

Conclusions

In summary, our results showed that there were no differences in ucMGP levels in CKD patients with preserved renal function (stage G1) and those who had mildly to significantly reduced renal function (stages G2 – G4). In patients with different CKD stages, ucMGP appears to be a good marker for increased cardiovascular risk, as its levels increase significantly in patients with CVD already in the early stages of the disease and correlate positively with age and the presence of CVD. Additionally, elevated serum levels of ucMGP showed strong correlations with SCr and Pi levels, which may be associated with an increased propensity to develop vascular calcification and fibrosis. We also found that ucMGP levels were significantly elevated in the male population with CKD compared to the female population, which is probably related to a higher cardiovascular risk in men.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
Informed consent from the humans, donors or donors' representatives: Department of Physiology and Pathophysiology, Medical University – Pleven.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

Borislav Ignatov – Formation of working groups, formation of participants' cards, access to medical documentation, processing of the results of, solving organizational issues, statistical processing of the obtained results, writing of articles. Tatyana Simeonova – Processing the results, solving organizational issues, statistical processing of the obtained results, writing articles. Tsvetelina Eftimova – Selection and clinical examination of patients. Anelia Dimitrova – Planning and control of the conducted research, analysis of the results and writing of reports and scientific articles. Krasimir Kostov – Processing of results, solving organizational issues, statistical processing of the obtained results, writing articles.

Author ORCIDs
Borislav Ignatov https://orcid.org/0000-0002-0325-6162
Tatyana Simeonova https://orcid.org/0000-0002-2307-1229
Tsvetelina Eftimova https://orcid.org/0000-0002-3606-1601
Anelia Dimitrova https://orcid.org/0000-0002-2010-0856
Krasimir Kostov https://orcid.org/0000-0003-2464-353X

Data availability
All of the data that support the findings of this study are available in the main text.

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