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## The association of serum dephosphorylated-uncarboxylated matrix gamma carboxyglutamate protein (dp-ucMGP) as a marker of vascular vitamin K status with allograft function in kidney transplant recipients

Vahideh Ebrahimzadeh Attari<sup>1</sup>, Zahra Shahvegharasl<sup>2</sup>, Pooya Fathalizadeh<sup>3</sup>, Sajjad Pourasghary<sup>4</sup>, Mohammadali Mohajel Shoja<sup>5</sup>, Sepideh Zunni Vahed<sup>3</sup>, Mohammadreza Ardalani<sup>3\*</sup>

<sup>1</sup>Maragheh University of Medical Sciences, Maragheh, Iran

<sup>2</sup>Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>3</sup>Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>4</sup>Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran

<sup>5</sup>Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA

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### ABSTRACT

**Introduction:** Kidney transplantation has considerably increased the survival and life quality of patients with end-stage renal disease.

**Objectives:** The current study was designed to investigate the circulating level of dephosphorylated-uncarboxylated matrix gamma carboxyglutamate protein (dp-ucMGP) as a marker of vitamin K status and vascular calcification in kidney transplant recipients as well as its association with the allograft function.

**Patients and Methods:** In this cross-sectional study, 90 eligible kidney transplant recipients were evaluated in the post-transplant phase (about 6-12 months after kidney transplantation). The serum levels of dp-ucMGP, urea, creatinine and other biochemical indices were determined.

**Results:** The mean serum level of dp-ucMGP was  $3.78 \pm 3.79$   $\mu\text{g/L}$ . Most of the participants (80%) had a normal range of serum dp-ucMGP ( $<4$   $\mu\text{g/L}$ ). However, 10 % had high serum dp-ucMGP ( $>12$   $\mu\text{g/L}$ ). Serum dp-ucMGP did not have any statistical significant association with serum urea, creatinine and kidney function ( $P > 0.05$ ).

**Conclusion:** Further epidemiologic studies are needed to assess the time trends of dp-ucMGP after renal transplant and its relation to kidney function, since high serum level of dp-ucMGP may make kidney transplant recipients prone to various cardiovascular disease (CVD) and transplant rejection.

### Implication for health policy/practice/research/medical education:

In a study on 90 kidney transplant recipients in the post-transplant phase, we found, the mean serum level of dephosphorylated-uncarboxylated matrix gamma carboxyglutamate protein (dp-ucMGP) was in normal range. However, a small percentage of participants had high serum dp-ucMGP ( $>12$   $\mu\text{g/L}$ ). Serum dp-ucMGP did not have any statistical significant association with serum urea, creatinine and kidney function, since previous studies showed high serum level of dp-ucMGP may make kidney transplant recipients susceptible to the cardiovascular events and transplant rejection.

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### Introduction

Kidney transplantation has considerably increased the survival and life quality of patients with end-stage renal disease (1-3). However, long-term consequences like cardiovascular disease (CVD) and vascular calcification

are still the leading cause of mortality after transplantation (4-8). Among different risk factors of CVD, there is some evidence for significant association between vitamin K deficiency and cardiovascular complications in patients with chronic kidney disease (9-11). It is also reported that

\*Corresponding author: Professor Mohammad Reza Ardalani, Email: ardalani34@yahoo.com and ardalani@tbzmed.ac.ir

vitamin K level may be low in kidney transplant recipients (12-14).

Vitamin K has a fundamental role in blood coagulation and carboxylation of gamma glutamate proteins including matrix gamma carboxyglutamate protein (MGP). MGP is expressed extensively in kidney because the serum level of its inactive form, dephosphorylated - uncarboxylated MGP (dp-ucMGP), is an indicator of vascular status of vitamin K and also vascular calcification (15-18).

It seems that micro-vascular property of kidney such as micro-albuminuria is inversely related to the circulating level of vitamin K and activated MGP levels (19). There is some evidence that serum level of dp-ucMGP is directly related to proteinuria and serum creatinine and inversely related to renal function (GFR, glomerular filtration rate) in patients with CKD (20-26).

### Objectives

The present study aimed to investigate the serum level of dp-ucMGP as a marker of vascular calcification and vitamin K status in kidney transplant recipients along with its relationship to the allograft function.

### Patients and Methods

#### *Study design and population*

The present cross-sectional investigation was conducted on kidney transplant recipients who were referred to Imam Reza hospital (Tabriz, Iran). The inclusion criteria were as follow; age 18 to 70 years old and appropriate kidney function (serum creatinine <1.6 mg/dL). The exclusion criteria were incidence of acute kidney rejection during the first month after transplantation, any history of major cardiovascular complications including myocardial infarction, congestive heart failure and stroke, affected by HIV, CMV and HBV, a history of thrombosis or coagulation disorders and or treatment with anticoagulants. Accordingly, a total of 90 patients were enrolled voluntarily within 6-12 months after kidney transplantation.

#### *Anthropometric and biochemical assessments*

General information on age, gender, transplantation type, education and smoking were asked from the participants at baseline. Subjects' height and weight were measured and the body mass index (BMI) was calculated [weight (kg)/height (m)<sup>2</sup>]. Blood pressure was measured in the right arm, in the seated position after five minutes' rest using an automated sphygmomanometer.

Venous blood samples were drawn after an overnight fast. Fasting blood sugar, serum urea, creatinine, cholesterol and triglyceride were analyzed by standard clinical laboratory methods. Serum levels of dp-ucMGP were measured using the human ELISA kit (Shanghai Crystal Day Biotech Co.,

Ltd., Shanghai, China) based on the principle of double-antibody sandwich technique. GFR as the best overall index of renal function was estimated based on the CKD-EPI (chronic kidney disease epidemiology collaboration) equation (2009) and the MDRD (modification of diet in renal disease study) equation using the online eGFR calculator of national kidney foundation ([https://www.kidney.org/professionals/KDOQI/gfr\\_calculator](https://www.kidney.org/professionals/KDOQI/gfr_calculator)).

#### *Ethical issues*

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of Tabriz University of Medical Sciences approved this study (Ethical code; IR.TBZMED.REC.1396.443). The informed consents were taken from the patients. Besides, this study was extracted from the M.D thesis of Pooya Fathalizadeh, (#58350) at this University.

#### *Statistical analysis*

Data were analyzed using SPSS software, version 21.0 (IBM Corp., Armonk, NY, USA). The normal distribution of variables was tested by the Kolmogorov–Smirnov test. Results were reported as mean (SD), otherwise it is stated. Regarding the nonparametric feature of serum MGP level, Spearman's rho correlation test was used to assess its relation with kidney function and other parameters. The significance level was set at  $P=0.05$ .

### Results

The general and demographic characteristics of patients are presented in Table 1. The mean age of participants was 44.1±13.05 years old. In the studied cases, 41.1% were women and 58.9% were men. The anthropometric and

**Table 1.** The demographic information of participants (n=90)

	No. (%)
Age*	44.1±13.05
Sex	
Women	37 (44.1%)
Men	53 (58.9%)
Transplant type	
Living donor	76 (84.4%)
Dead brain donor	14 (15.6%)
Smoking	
Yes	80 (88.9%)
No	10 (11.1%)
Literacy	
Illiterate	19 (21.1%)
Under diploma	37 (41.1%)
Diploma	22 (24.4%)
Undergraduate degree	3 (3.3%)
Bachelor and higher	9 (10%)

\*Mean ± SD

biochemical characteristics of patients are summarized in Table 2. The mean body weight changes within 6-12 months (average  $7.46 \pm 1.65$  months) after transplantation was about  $4.06 \pm 7.45$  kg. The mean BMI was  $25.77 \pm 4.42$  kg/m<sup>2</sup>, indicating the overweight of patients after kidney transplantation.

The mean serum levels of urea and creatinine were  $38.78 \pm 12.19$  mg/dL and  $1.26 \pm 0.25$  mg/dL, respectively. The estimated GFR (eGFR) was  $63.62 \pm 15.02$  mL/min/1.73m<sup>2</sup> based on the CKD-EPI formula and was  $57.45 \pm 12.61$  mL/min/1.73 m<sup>2</sup> based on the MDRD formula. The median (IQR) of serum level of dp-ucMGP was reported as 2.40 (1.60-3.20) µg/L. Most of the participants (eighty percent) had a normal range of serum dp-ucMGP (<4 µg/L). However, 10 % had high serum dp-ucMGP (>12 µg/L).

The association of serum dp-ucMGP with kidney function is presented in Table 3. Serum dp-ucMGP did not have any statistically significant relationship with serum urea, serum creatinine, eGFR-EPI and eGFR-MDRD ( $P > 0.05$ ). Moreover, no significant association of serum dp-ucMGP and any other baseline parameters including weight and blood pressure was detected ( $P > 0.05$ ; Table 4).

## Discussion

Vascular calcification is an important predictor of CVD and a possible pathologic factor in transplant rejection (27-29). There are different risk factors for development of coronary artery calcification (CAC) after transplantation including immunosuppressive therapy (30), post-transplant diabetes, lower 25(OH) D3 level, high serum triglyceride, high diastolic blood pressure, Caucasian race and high BMI (31-32). The circulating level of dp-ucMGP

**Table 2.** The anthropometric and serum biochemical characteristics of participants (n=90)

	Mean ± SD
Weight (kg)	69.61±11.59
Weight diff*	4.06±7.45
BMI	25.77±4.42
SBP (mm Hg)	122.93±11.39
DBP (mm Hg)	76.41±9.36
FBS (mg/dL)	108.26±34.65
Total cholesterol	187.48±43.6
Triglyceride	189.39±114.79
Urea (mg/dL)	38.78±12.19
Creatinine (mg/dL)	1.26±0.25
eGFR-EPI (mL/min/1.73 m <sup>2</sup> )	63.62±15.02
eGFR-MDRD (mL/min/1.73 m <sup>2</sup> )	57.45±12.61
dp-uc MGP (µg/L)**	2.40 (1.60-3.20)

\* Weight differences after transplantation.

\*\* Data are presented as median (25th, 75th percentiles).

**Table 3.** The association of serum dp-ucMGP with kidney function

	r	P value*
Serum urea	0.132	0.248
Serum creatinine	0.075	0.511
eGFR-EPI	-0.088	0.395
eGFR-MDRD	-0.097	0.439

\*\*P values are based on the Spearman's rho correlation test.

**Table 4.** The association of serum dp-ucMGP with some baseline parameters

	r	P value*
Sex	0.094	0.411
Age	0.125	0.271
Weight	0.114	0.319
Weight diff	-0.013	0.909
BMI	0.047	0.686
FBS	0.083	0.557
Total cholesterol	-0.100	0.453
Triglyceride	-0.188	0.159
SBP	0.101	0.377
DBP	0.107	0.353

\*\*P values are based on the Spearman's rho correlation test.

considers as a relatively new marker of vascular vitamin K status and also vascular calcification. Decreased vitamin K consumption and increased serum dp-ucMGP level are common in kidney transplant recipients which can affect kidney function and cardiovascular consequences (33).

Some evidence revealed a significant reverse relation between dp-ucMGP and kidney function (9,13,21,34). Results of a cohort study showed that kidney transplant recipients at the highest quartile of dp-ucMGP had a higher risk of developing transplant failure and mortality risk (13). Recently, Puzantian et al significantly reported that dp-ucMGP level was progressively increased in CKD patients with decreasing renal function (35). However, according to our results, the association of serum dp-ucMGP with kidney function was not statistically significant in kidney transplant recipients.

Vitamin K exists in two forms of phyloquinone (K1) and menaquinone (K2), respectively, in plant and animal foods. As the intake of vegetables, meat and dairy products decrease in patients with CKD due to the restriction of foods, it seems that vitamin K intake is low in these patients (9,19). After transplantation some of these restrictions are still continued (12,33).

Results of Boxma et al showed that in kidney transplant recipients with stable renal function, total vitamin K intake was low, dp-ucMGP levels were high and risk of arterial calcification was increased during 75 months after transplantation (33). During a randomized clinical trial,

Holden et al showed that vitamin K supplementation in hemodialysis patients could decrease the development of CAC and also mortality rate (36). In another study, vitamin K1 supplementation in hemodialysis patients led to reduction of inactive MGP levels and also the vascular calcification (37).

Although the definition of high dp-ucMGP concentration differed across the studies, most of them considered the cut-point of more than 400 pmol/L up to more than 1977 pmol/L as high dp-ucMGP level depending on their population (38). As the MGP activity depends on some factors such as its genetic polymorphism, it is important to assess the association of MGP with those discussed assumptions in different populations.

### Conclusion

To our knowledge, this is the first time that the circulating level of dp-ucMGP and its relation with kidney function in kidney transplant recipients have been assessed in the Iranian population. According to our results, the mean serum level of dp-ucMGP was in normal range. However, a small percentage of participants had high serum dp-ucMGP (more than 12 µg/L). Serum dp-ucMGP did not have any statistical significant association with serum urea, creatinine and kidney function. High serum level of dp-ucMGP may make kidney transplant recipients susceptible to cardiovascular events and transplant rejection. Therefore, further epidemiologic studies are needed to assess time trends of dp-ucMGP after renal transplant and its relation with kidney function.

### Study limitations

Unfortunately, during the present study, we cannot assess the pulse wave velocity as a measure of arterial stiffness and vascular calcifications (Kauppila score). Moreover, the other limitations of this study were the low sample size and lack of the evaluation of serum total MGP levels.

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### Authors' contribution

VEA contributed to design of the study, gathering the patients, data entering and data analysis and also preparing the manuscript. MRA, MMS, and SZV cooperated in design of the study, selecting the patients and final edition. ZSH prepared the primary draft of article. PF and SP contributed to gathering the patients. All authors read and signed the paper manuscript.

### Conflicts of interests

The authors declared that there was no conflict of interest.

### Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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