www.nephropathol.com DOI: 10.34172/jnp.2020.24 J Nephropathol. 2020;9(3):e24

Journal of Nephropathology

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[1], Zahra Shahvegharasl[2], Pooya Fathalizadeh[3], Sajjad Pourasghary[4], Mohammadali Mohajel Shoja[5], Bahram Niknafs[3], Mohammadreza Ardalan[3*]

[1]Maragheh University of Medical Sciences, Maragheh, Iran
[2]Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran
[5]Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 2 September 2019
Accepted: 7 November 2019
Published online: 25 November 2019

Keywords:
Matrix Gla protein, Kidney function, Kidney transplant, Vascular calcification, Vitamin K, End-stage renal disease, Chronic kidney disease, Cardiovascular disease

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±3.79 µg/L. Most of the participants (80%) had a normal range of serum dp-ucMGP (<4 µg/L). However, 10 % had high serum dp-ucMGP (>12 µg/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 µg/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.

Please cite this paper as: Ebrahimzadeh Attari V, Shahvegharasl Z, Fathalizadeh P, Pourasghary S, Mohajel Shoja M, Niknafs B, Ardalan M. 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. J Nephropathol. 2020;9(3):e24. DOI: 10.34172/jnp.2020.24.

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 vascular calcification in patients with chronic kidney disease (9-11). It is also reported that

*Corresponding author: Professor Mohammadreza Ardalan, Email: ardalan34@yahoo.com and ardalanm@tbzmed.ac.ir

Original Article

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 and serum level of its inactive form, dephosphorylated - uncarboxylated MGP (dp-ucMGP), is an indicator of vitamin K and also vascular calcification (15-18).

It seems that micro-vascular dysregulation 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 potential 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 of Transplant Center-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: acute kidney rejection during the first month after transplantation, any history of major cardiovascular complications including myocardial infarction, congestive heart failure and stroke, active HIV, CMV and HBV infection, a history of thrombosis or coagulation disorders and contemporary treatment with anticoagulants. During our study, total number of 90 patients were enrolled within their 6-12 months of kidney transplantation.

Anthropometric and biochemical assessments

General information including age, gender, transplantation type, education and smoking were asked from the participants, height and weight were measured and the body mass index (BMI) was calculated [weight (kg)/height (m)^2]. 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 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).

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. This study was extracted from the M.D thesis of Pooya Fathalizadeh, (#58350) at Tabriz University of Medical Sciences.

Statistical analysis

Data were analyzed using SPSS software, version 16.0 (IBM Corp., Armonk, NY, USA). The normal distribution of variables was tested by the Kolmogorov–Smirnov test. Results were reported as mean (SD) or median (25th, 75th percentiles). 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 $P \leq 0.05$.

Results

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 biochemical

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%)
Brain-death 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

characteristics of patients are summarized in Table 2. Mean body weight changes within 6-12 months (average 7.46±1.65 months) after transplantation was about 4.06±7.45 kg, and their mean BMI was 25.77±4.42 kg/m^2, indicating the overweight trend after kidney transplantation.

The mean serum levels of urea and creatinine were 38.78±12.19 mg/dL and 1.26±0.25 mg/dL, respectively. The estimated GFR (eGFR) was 63.62±15.02 mL/min/1.73m^2 based on the CKD-EPI formula and was 57.45±12.61 ml/min/1.73 m^2 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% of them 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 with 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 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 alograft 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.

Vitamin K exists in two forms of phylloquinone (K1) and menaquinone (K2), respectively, in plant and animal foods. As the intake of vegetables, meat and dairy products are encouraged to be decreased in CKD patients, it seems that vitamin K intake is low in these patients (9,19). Even after transplantation some of these restrictions are still continued and extend the domain of vitamin K deficiency to post-transplant era (12,33).

Results of Boxma et al in a group of kidney transplant recipients with stable alograft function, showed that they had low vitamin K intake, their plasma dp-ucMGP levels were high and they had an increased risk of arterial

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^2)	63.62±15.02
eGFR–MDRD (mL/min/1.73 m^2)	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.

calcification (33). During a randomized clinical trial, Holden et al showed that vitamin K supplementation in hemodialysis patients could decrease the development of CAC and mortality among this group (36). Vitamin K1 supplementation by reduction of inactive MGP level imposes this positive effect (37).

The definition for high dp-ucMGP is diffident because the results come from various studies population (38). As an additional words, because MGP activity depends on genetic background, the importance of its measurement and normal value definition in different population became more obvious.

Conclusion

To our knowledge, this is the first study that measures the circulating level of dp-ucMGP and its relation with alograft function in kidney transplant recipients. 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.

Limitations of the study

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.

Acknowledgments

We wish to express our appreciation to the subjects who participated in the study.

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 interest

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.

Funding/Support

This study was supported by a grant from the Research Vice-Chancellor and kidney Research Center of Tabriz University of Medical Sciences, Tabriz, Iran.

References

1. Junchotikul P, Charoenthanakit C, Saiyud A, Parapiboon W, Ingsathit A, Jirasiritham S, et al. Assessment of the changes in health-related quality of life after kidney transplantation in a cohort of 232 thai patients. Transplant Proc. 2015;47:1732-5. doi: 10.1016/j.transproceed.2015.02.018.
2. Haller M, Gutjahr G, Kramar R, Harnoncourt F, Oberbauer R. Cost-effectiveness analysis of renal replacement therapy in Austria. Nephrol Dial Transplant. 2011;26:2988-95. doi: 10.1093/ndt/gfq780.
3. Kostro JZ, Hellmann A, Kobiela J, Skóra I, Lichodziejewska-Niemierko M, Dębska-Ślizień A, et al. Quality of life after kidney transplantation: a prospective study. Transplant Proc. 2016;48:50-4. doi: 10.1016/j.transproceed.2015.10.058.
4. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant. 2004;4:1289-95. doi: 10.1111/j.1600-6143.2004.00515.x.
5. Dounousi E, Leivaditis K, Eleftheriadis T, Liakopoulos V. Osteoporosis after renal transplantation. Int Urol Nephrol. 2015;47:503-11. doi: 10.1007/s11255-014-0862-3.
6. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011;378:1419-27. doi: 10.1016/S0140-6736(11)61334-2.
7. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2012;60:434-80. doi: 10.1016/j.jacc.2012.05.008.
8. Khoshdel AR, Carney SL. Arterial stiffness in kidney transplant recipients: an overview of methodology and applications. Urol J. 2008;5:3-14.
9. Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, Kaczmarska M, Stefańczyk L, Vermeer C, et al. Plasma desphospho-uncarboxylated matrix Gla protein as a marker of kidney damage and cardiovascular risk in advanced stage of chronic kidney disease. Kidney Blood Press Res. 2016;41:231-9. doi: 10.1159/000443426.
10. Holden RM, Morton AR, Garland JS, Pavlov A, Day AG, Boot SL. Vitamins K and D status in stages 3–5 chronic kidney disease. Clin J Am Soc Nephrol. 2010;5:590-7. doi: 10.2215/CJN.06420909
11. Cranenburg EC, Schurgers LJ, Uiterwijk HH, Beulens JW, Dalmeijer GW, Westerhuis R, et al. Vitamin K intake and status are low in hemodialysis patients. Kidney Int.

2012;82:605-10. doi: 10.1038/ki.2012.191.
12. van den Berg E, Boxma PI, Geleijnse JM, Laverman GD, Schurgers LJ, Vermeer C, et al. Vitamin K intake and plasma desphospho-uncarboxylated matrix Gla-protein levels in renal transplant recipients. Nutrition and Cardiovascular Health in Renal Transplant Recipients. 2013;7:113.
13. Keyzer CA, Vermeer C, Joosten MM, Knapen MH, Drummen NE, Navis G, et al. Vitamin K status and mortality after kidney transplantation: a cohort study. Am J Kidney Dis. 2015;65:474-83. doi: 10.1053/j.ajkd.2014.09.014.
14. Riphagen IJ, Keyzer CA, Drummen NEA, de Borst MH, Beulens JWJ, Gansevoort RT, et al. Prevalence and effects of functional vitamin K insufficiency: the PREVEND study. Nutrients. 2017;9:E1334. doi: 10.3390/nu9121334.
15. Wei FF, Drummen NEA, Schutte AE, Thijs L, Jacobs L, Petit T, et al. Vitamin K dependent protection of renal function in multi-ethnic population studies. EBioMedicine. 2016;4:162-9. doi: 10.1016/j.ebiom.2016.01.011.
16. Cranenburg EC, Koos R, Schurgers LJ, Magdeleyns EJ, Schoonbrood TH, Landewé RB, et al. Characterisation and potential diagnostic value of circulating matrix Gla protein (MGP) species. Thromb Haemost. 2010;104:811-22. doi: 10.1160/TH09-11-0786.
17. Schurgers LJ, Teunissen KJ, Knapen MH, Kwaijtaal M, van Diest R, Appels A, et al. Novel conformation-specific antibodies against matrix gamma-carboxyglutamic acid (Gla) protein: undercarboxylated matrix Gla protein as marker for vascular calcification. Arterioscler Thromb Vasc Biol. 2005;25:1629-33.
18. Rennenberg RJ, de Leeuw PW, Kessels AG, Schurgers LJ, Vermeer C, van Engelshoven JM, et al. Calcium scores and matrix Gla protein levels: association with vitamin K status. Eur J Clin Invest. 2010;40:344-9. doi: 10.1111/j.1365-2362.2010.02275.x.
19. van den Heuvel EG, van Schoor NM, Lips P, Magdeleyns EJ, Deeg DJ, Vermeer C, et al. Circulating uncarboxylated matrix Gla protein, a marker of vitamin K status, as a risk factor of cardiovascular disease. Maturitas. 2014;77:137-41. doi: 10.1016/j.maturitas.2013.10.008.
20. Puzantian H, Akers SR, Oldland G, Javaid K, Miller R, Ge Y, et al. Circulating dephospho-uncarboxylated matrix Gla-protein is associated with kidney dysfunction and arterial stiffness. Am J Hypertens. 2018;31:988-94. doi: 10.1093/ajh/hpy079.
21. Mansour AG, Hariri E, Daaboul Y, Korjian S, El Alam A, Protogerou AD, et al. Vitamin K2 supplementation and arterial stiffness among renal transplant recipients-a single-arm, single-center clinical trial. J Am Soc Hypertens. 2017;11:589-97. doi: 10.1016/j.jash.2017.07.001.
22. Fain ME, Kapuku GK, Paulson WD, Williams CF, Raed A, Dong Y, et al. Inactive matrix Gla protein, arterial stiffness, and endothelial function in African American hemodialysis patients. Am J Hypertens. 2018;31:735-41. doi: 10.1093/ajh/hpy049.
23. Parker BD, Ix JH, Cranenburg ECM, Vermeer C, Whooley MA, Schurgers LJ. Association of kidney function and uncarboxylated matrix Gla protein: Data from the Heart and Soul Study. Nephrol Dial Transplant. 2009;24:2095-101. doi: 10.1093/ndt/gfp024.
24. Moe SM, Reslerova M, Ketteler M, O'neill K, Duan D, Koczman J, et al. Role of calcification inhibitors in the pathogenesis of vascular calcification in chronic kidney disease (CKD). Kidney Int. 2005;67:2295-304. doi: 10.1111/j.1523-1755.2005.00333.x.
25. Mazzaferro S, Pasquali M, Pugliese F, Barresi G, Carbone I, Francone M, et al. Serum levels of calcification inhibition proteins and coronary artery calcium score: comparison between transplantation and dialysis. Am J Nephrol. 2007;27:75-83. doi: 10.1159/000099095.
26. Schurgers LJ, Barreto DV, Barreto FC, Liabeuf S, Renard C, Magdeleyns EJ, et al. The circulating inactive form of matrix gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. Clin J Am Soc Nephrol. 2010;5:568-75. doi: 10.2215/CJN.07081009.
27. DeLoach SS, Joffe MM, Mai X, Goral S, Rosas SE. Aortic calcification predicts cardiovascular events and all-cause mortality in renal transplantation. Nephrol Dial Transplant. 2009;24:1314-9. doi: 10.1093/ndt/gfn753.
28. Nguyen PT, Henrard S, Coche E, Goffin E, Devuyst O, Jadoul M. Coronary artery calcification: a strong predictor of cardiovascular events in renal transplant recipients. Nephrol Dial Transplant. 2010;25:3773-8. doi: 10.1093/ndt/gfq268.
29. Gwinner W, Suppa S, Mengel M, Hoy L, Kreipe HH, Haller H, et al. Early calcification of renal allografts detected by protocol biopsies: causes and clinical implications. Am J Transplant. 2005;5:1934-41. doi: 10.1111/j.1600-6143.2005.00938.x.
30. Nickel T, Schlichting CL, Weis M. Drugs modulating endothelial function after transplantation. Transplantation. 2006;82:S41-6. doi: 10.1097/01.tp.0000231505.91988.26.
31. Westenfeld R, Schlieper G, Wöltje M, Gawlik A, Brandenburg V, Rutkowski P, et al. Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis--implications for post-transplantation bone disease. Nephrol Dial Transplant. 2011;26:4115-23. doi: 10.1093/ndt/gfr214.
32. Cianciolo G, Capelli I, Angelini ML, Valentini C, Baraldi O, Scolari MP, et al. Importance of vascular calcification in kidney transplant recipients. Am J Nephrol. 2014;39:418-426. doi: 10.1159/000362492.
33. Boxma PY, van den Berg E, Geleijnse JM, Laverman GD, Schurgers LJ, Vermeer C, et al. Vitamin k intake and plasma desphospho-uncarboxylated matrix Gla-protein levels in kidney transplant recipients. PLoS One. 2012; 7:e47991. doi: 10.1371/journal.pone.0047991
34. Schurgers LJ, Barreto DV, Barreto FC, Liabeuf S, Renard C, Magdeleyns EJ, et al. The circulating inactive form of matrix Gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. Clin J Am Soc Nephrol. 2010;5:568-75. doi: 10.2215/CJN.07081009.
35. Puzantian H, Akers SR, Oldland G, Javaid K, Miller R, Ge Y, et al. Circulating dephospho-uncarboxylated matrix Gla-protein is associated with kidney dysfunction and drterial stiffness. Am J Hypertens. 2018;31:988-994. doi: 10.1093/ajh/hpy079.

36. Holden RM, Booth SL, Day AG, Clase CM, Zimmerman D, Moist L, et al. Inhibiting the progression of arterial calcification with vitamin K in HemoDialysis patients (iPACK-HD) trial: rationale and study design for a randomized trial of vitamin K in patients with end stage kidney disease. Can J Kidney Health Dis. 2015;2:17. doi: 10.1186/s40697-015-0053-x.
37. Krueger T, Schlieper G, Schurgers L, Cornelis T, Cozzolino M, Jacobi J, et al. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol. Nephrol Dial Transplant. 2014;29:1633-8. doi: 10.1093/ndt/gft459.
38. Lees JS, Chapman FA, Witham MD, Jardine AG, Mark PB. Vitamin K status, supplementation and vascular disease: a systematic review and meta-analysis. Heart. 2019;105:938-945. doi:10.1136/heartjnl-2018-313955