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Research Article

Vitamin K2 supplementation and arterial stiffness among renal transplant recipients—a single-arm, single-center clinical trial

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Abstract

Subclinical vitamin K deficiency is prevalent among renal transplant recipients and is associated with an increased risk of cardiovascular disease. However, the association between vitamin K supplementation and improvement of arterial stiffness has not been explored in the renal transplant population. The KING trial (vitamin K2 In reNal Graft) is a single-arm study that evaluated the association between the change in vitamin K status and indices of arterial stiffness following 8 weeks of menaquinone-7 (vitamin K2) supplementation (360 μg once daily) among renal transplant recipients (n = 60). Arterial stiffness was measured using carotid-femoral pulse wave velocity (cfPWV). Subclinical vitamin K deficiency was defined as plasma concentration of dephosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP) >500 pmol/L.At baseline, 53.3% of the study subjects had subclinical vitamin K deficiency. Supplementation was associated with a 14.2% reduction in mean cfPWV at 8 weeks (cfPWV pre-vitamin K2 = 9.8 ± 2.2 m/s vs. cfPWV post-vitamin K2 = 8.4 ± 1.5 m/s; $P < .001$). Mean dp-ucMGP concentrations were also significantly reduced by 55.1% following menaquinone-7 supplementation with a reduction in the prevalence of subclinical deficiency by 40% ($P = .001$). When controlled for age, durations of hemodialysis and transplantation, and the change in 24-hour mean arterial pressure, the improvement in arterial stiffness was independently associated with the reduction in dp-ucMGP concentration ($P = .014$).Among renal transplant recipients with stable graft function, vitamin K2 supplementation was associated with improvement in subclinical vitamin K deficiency and arterial stiffness. (Clinicaltrials.gov: NCT02517580). J Am Soc Hypertens 2017;■(■):1–9.

Keywords: Menaquinone; pulse wave velocity.

Clinical Trial Acronym: KING.

Registration number: Clinicaltrials.gov: NCT02517580.

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Introduction

Renal transplantation is associated with considerably better cardiovascular (CV) outcomes and quality of life among patients with end-stage renal disease (ESRD) when compared with other renal replacement modalities.[1] This improvement is related to the restoration of renal function conferred by the transplanted graft.[2] However, the rate of CV events remains significantly higher among renal transplant recipients as compared with age- and sex-matched subjects in the general population, in part due to arterial stiffness and the active vascular calcification that persist following kidney transplantation.[3–5]

Vascular calcification is an active and well-regulated biological process promoted by an imbalance between procalcific and calcification inhibiting substances leading to osteogenesis.[6] Irrespective of the histoanatomic and etiological characteristics of vascular calcifications, decreased activity of endogenous calcification inhibitors, such as the potent matrix Gla protein (MGP), enables mineralization of the vascular wall. MGP is a small, approximately 10-kDa protein that is expressed primarily by osteoclasts, chondrocytes, and vascular smooth muscle cells. Its activation confers the calcification inhibitory activity and depends on two post-translational processes: the vitamin K–dependent glutamate carboxylation and serine phosphorylation.[6–8] Active MGP (phosphorylated and carboxylated) inhibits local crystal growth and vascular smooth muscle cell apoptosis, while dephosphorylated-uncarboxylated MGP (dp-ucMGP) is inactive, has low affinity for calcium, and is then released in the circulation.[6,9] Studies have demonstrated that plasma levels of dp-ucMGP are markers of vascular vitamin K status—with high levels indicating vascular vitamin K deficiency—and are positively associated with arterial stiffness.[8,10] There is growing evidence that most hemodialysis patients have subclinical vitamin K deficiency[11–13] and that supplementation with vitamin K decreases markedly circulating levels of inactive MGP.[13–15] More recently, vitamin K insufficiency was shown to be highly prevalent in stable renal transplant subjects, and it was associated with increased mortality risk.[16,17] Supplementation of vitamin K has been previously associated with a dose-dependent reduction in circulating dp-ucMGP and improved arterial stiffness among healthy adults and among ESRD patients on hemodialysis, but this association among renal transplant recipients has not yet been explored.[14,15,18]

Supplementation of vitamin K among renal transplant patients is postulated to be associated with reduction in dp-ucMGP and subsequent improvement in arterial stiffness. The KING trial (vitamin K2 In reNal Graft) is a single-arm pilot study that evaluated the association between vitamin K2 supplementation and the change in both subclinical vitamin K status and indices of arterial stiffness among 60 renal transplant recipients with stable graft function.

Methods

Study Design, Settings, and Participants

KING was a prospective, single-center, single-arm trial (ClinicalTrials.gov identifier: NCT02517580). Between April 2015 and May 2016, we consecutively screened men and women, 18 years of age or older, who had a functional renal graft and presented for follow-up at the Lebanese American University Medical Center. Inclusion criteria included stable renal function for at least 3 months. Exclusion criteria included a history of a thrombotic or CV event in the past month prior to enrollment, known coagulopathy, atrial fibrillation, current or planned pregnancy or lactation, soy allergy, concomitant or recent administration of any vitamin K–containing supplement within 6 months of enrollment, active warfarin therapy, and known intestinal malabsorption or hypomotility syndromes. Informed consent was obtained from all participating subjects. The Institutional Review Board of the Lebanese American University approved the trial protocol (approval number: LAU.SOM.SB1.16/April/2015). The trial was in accordance with the 1964 Helsinki declaration and its later amendments. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Baseline measures of carotid-femoral pulse wave velocity (cfPWV), 24-hour peripheral (brachial) pressures, and central hemodynamics (aortic pressures and augmentation index) were obtained at enrollment. Additionally, baseline information regarding past medical history, comorbidities, and details of the renal graft were gathered from chart review. All patients received oral menaquinone-7 (MK-7) (MenaQ7; NattoPharma, Hovik, Norway), as a source of vitamin K2, once daily at a dose of 360 μg for a total of 8 weeks. Patients were contacted by telephone once weekly to document supplement adherence and to monitor for the development of treatment emergent adverse events (TEAEs). At 8 weeks, patients then returned for a follow-up visit within 2 days of supplement discontinuation for follow-up hemodynamic and laboratory measurements. Following the active treatment period, a 2-week safety period ensued to monitor for adverse events. The total study duration was 10 weeks (8 weeks of active supplementation + 2 weeks of safety follow-up) (Figure 1). All participants provided written informed consent prior to enrollment.

Outcomes

The prespecified primary end point of this study was the change from baseline in cfPWV at 8 weeks following MK-7 supplementation. Secondary end points included change from baseline in 24-hour brachial and central hemodynamics (brachial and aortic pressures and augmentation

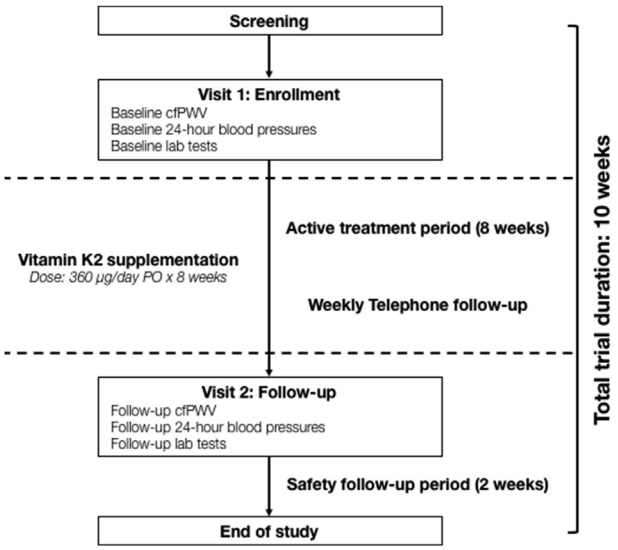

Figure 1. Study design.

index), change from baseline in blood concentration of dp-ucMGP at 8 weeks, as well as the association between changes in arterial stiffness measures and vitamin K deficiency. All end points were evaluated in the primary analysis population, defined as all enrolled patients who had measurements at both baseline and 8 weeks. TEAEs were recorded following enrollment up to 2 weeks after the discontinuation of MK-7 supplementation at 8 weeks (total of 10 weeks after enrollment). All TEAEs were reported in the safety population, defined as all enrolled patients who had received at least one dose of the vitamin K2 supplement.

Measurements

Arterial stiffness was evaluated by measurement of cfPWV at baseline and at follow-up using Complior Analyse (Alam Medical, France). cfPWV is a noninvasive, reproducible technique that has previously been used as a surrogate of CV disease in the kidney transplant population and is considered the gold standard to directly measure arterial stiffness. A detailed description of the cfPWV technique has previously been described.[19] Twenty-four–hour hemodynamic studies, namely brachial (peripheral) and aortic (central) blood pressure and augmentation index, were evaluated using an extensively validated brachial oscillometric ambulatory technique (Mobil-O-Graph, IEM, Stolberg, Germany), as previously described.[20] The aortic hemodynamic parameters were assessed by software analysis after the data were downloaded to the manufacturer's Hypertension Measurement Software (version 4.6). In brief, following each conventional oscillometric blood pressure measurement, the brachial pressure waves were recorded by keeping the brachial cuff inflated at the diastolic blood pressure level for roughly 10 seconds. Based on invasive and clinical validation data, the mean and diastolic brachial blood pressure were selected for brachial blood pressure waveforms calibration in order to assess aortic systolic blood pressure.[20,21]

Patients' sera were obtained at baseline and follow-up for laboratory testing. All patients had a laboratory testing panel at baseline consisting of a complete blood count, chemistry panel, lipid panel, liver function tests, albumin, globulin, uric acid, C-reactive protein, parathyroid hormone, vitamin D, and creatine phosphokinase. Plasma was also used to measure levels of dp-ucMGP using inaKtif MGP Kit (Immunodiagnostic Systems, Boldon, UK). Subclinical vitamin K deficiency was defined as plasma concentration of dp-ucMGP >500 pmol/L, which was consistent with the definition used in prior studies.[16,22] All laboratory tests were performed in a central laboratory.

Statistical Analysis

Data were analyzed using Stata 13 (StataCorp LP, TX, USA). Characteristics of the study population were evaluated using descriptive statistics. Data were expressed as frequencies and percentages for categorical variables, means ± standard deviation for parametric continuous variables, and median and interquartile range for nonparametric continuous variables. Paired t-test was performed to evaluate the univariate association between measures of pre- and post-vitamin K supplementation. Multiple linear regression was also performed to evaluate the association between the change in dp-ucMGP concentrations and the change in indices of arterial stiffness from baseline to 8 weeks following MK-7 supplementation. The change in clinical parameters and cfPWV was defined as the value post-vitamin K2 supplementation minus the value pre-vitamin K2 supplementation. Parameters that have either been historically associated with arterial stiffness such as age; gender; the presence of classical CV risk factors such as hypertension, hyperlipidemia, smoking, and diabetes mellitus; as well as duration of time on hemodialysis prior to transplantation were tested in the univariate analysis. Variables with a P-value $< .10$ in the univariate paired t-test analysis were included in the multiple regression model. Furthermore, to determine potential treatment effect modification based on baseline vitamin K status, a nonprespecified subgroup analysis was conducted, and P-value of interaction was calculated.

The sample size was calculated to provide 85% power for the 1 m/s reduction in cfPWV at the one-sided $\alpha = 0.025$ level (ie, $\alpha = 0.05$ at the two-sided level) with an estimated difference in standard deviation of 2.4 m/s. It has previously been demonstrated that a cfPWV change $\geq$0.5 m/s is considered clinically relevant.[23,24] To estimate the sample size, databases from prior studies (both published and unpublished) of arterial stiffness in renal transplant patients were used.[19] Assuming that 10% of patients will not be evaluable for the primary outcome, the final estimated sample size was n = 60 subjects.

Results

From April 2015 through May 2016, a total of 60 patients were enrolled (Figure 2). The study population was 56.7% male with a mean age of 49.7 ± 10.4 years. Baseline characteristics are summarized in Table 1. A total of four patients (6.7%) withdrew consent. No patients were lost to follow-up during the course of the study (Figure 2). Among all enrolled patients, 50% of patients were hypertensive, 20% were diabetic, and 13.3% had a prior history of CV events, defined as prior history of either acute coronary syndrome, stroke, or symptomatic peripheral artery disease. Subclinical vitamin K deficiency, as measured by dp-ucMGP, was prevalent at baseline among 32 patients (53.3%). Overall, 56 (93.3%) had both pre- and post-MK-7 supplementation PWV measurements and were evaluable for the primary efficacy outcome.

Among patients who were included in the primary analysis population, the mean baseline cfPWV was 9.8 ± 2.2 m/s. Compared with baseline measurements, the mean 8-week follow-up cfPWV was 8.4 ± 1.5 m/s, demonstrating a significant 1.4 m/s absolute decrease in cfPWV (14.2% relative reduction) following MK-7 supplementation ($P < .0001$). This reduction was mirrored by a significant decrease in 24-hour peripheral and central blood pressures [mean arterial pressure (MAP): 2.3 mm Hg absolute reduction, $P = .014$], but not in 24-hour augmentation index ($P = .70$) (Table 2). Concomitantly, mean dp-ucMGP concentration was significantly reduced after MK-7 supplementation, with a 55.1% relative reduction in dp-ucMGP concentration as compared with the baseline values (556.9 pmol/L vs. 249.7 pmol/L; $P < .0001$). After supplementation, the prevalence of subclinical vitamin K deficiency decreased to 13.3%.

To evaluate the association between the arterial stiffness and vitamin K status, a multivariate regression model controlling for patient age, duration of hemodialysis and transplantation, and the change in 24-hour central MAP from baseline to 8 weeks was conducted. The improvement in dp-ucMGP was independently associated with the reduction in cfPWV ($P = .014$) (Figure 3, Table 3). Given a significant observed change in both creatinine and albumin pre- and post-K2 supplementation, a second multivariate regression was performed that included the same variables in the initial model with the addition of albumin and creatinine to adjust for the observed differences. Similarly, a significant independent association was observed between the improvement in dp-ucMGP and the reduction in cfPWV ($P = .026$).

In an additional exploratory analysis, baseline vitamin K status significantly modified the impact of dp-ucMGP change on the improvement in arterial stiffness (P-value for interaction = 0.029). When subgrouped by baseline vitamin K status, the association between the change in cfPWV and the change in dp-ucMGP was significant only among patients with baseline vitamin K deficiency ($P = .03$), but not among patients with normal baseline vitamin K status ($P = .25$). This relationship was consistent in the univariate model, as well as in the multivariate model when controlling for patient age, duration of hemodialysis and transplantation, and change in MAP from baseline to 8 weeks (Table 3).

In the safety population, MK-7 supplementation was generally well tolerated. There were no life-threatening

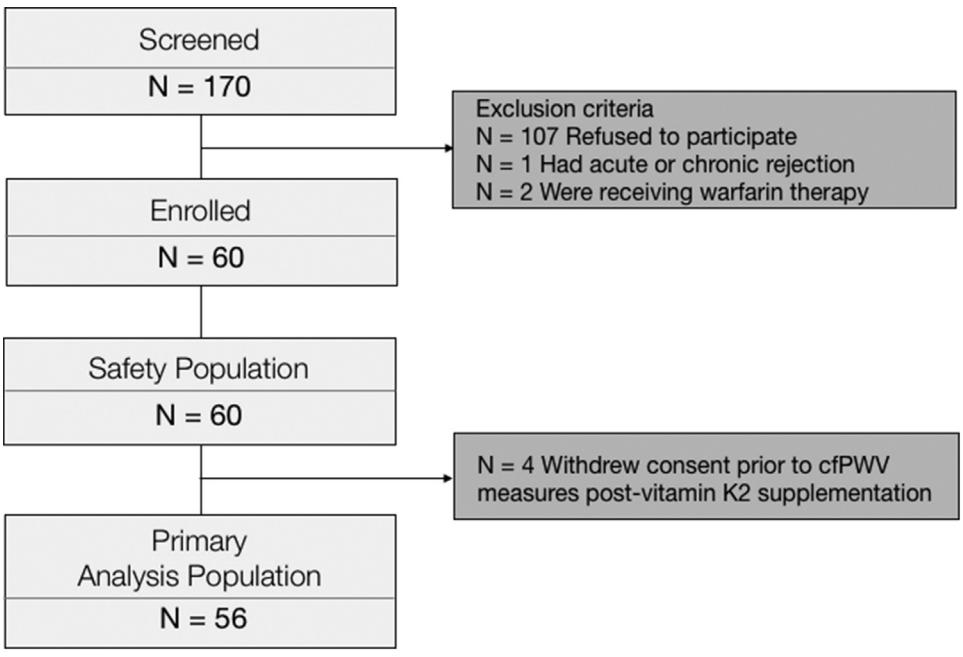

Figure 2. Study flow diagram.

Table 1
Baseline characteristics of the study population

Characteristic	Value (N = 60*)
Age (y), mean ± SD	49.7 ± 10.4
Male gender, % (n)	56.7 (34)
Age at transplantation (y), mean ± SD	33.7 ± 12.0
Transplant duration (y), mean ± SD	15.9 ± 6.0
Hemodialysis duration (mo), mean ± SD	25.2 ± 31.2
Hypertension, % (n)	50.0 (30)
Diabetes mellitus, % (n)	20.0 (12)
Prior history of cardiovascular events,† % (n)	13.3 (8)
Prior history of coronary artery disease, % (n)	11.7 (7)
Prior history of stroke, % (n)	0
Prior history of symptomatic PAD, % (n)	3.3 (2)
Hypercholesterolemia, % (n)	50 (30)
Hypertriglyceridemia, % (n)	33.3 (22)
Active smoking, % (n)	26.7 (16)

PAD, peripheral artery disease; SD, standard deviation.
* N reported for all patients enrolled in the study.
† Prior history of cardiovascular event was defined as history of acute coronary syndrome, cerebrovascular event, or acute peripheral ischemic event.

adverse events reported either during the 8 weeks of active treatment or the 2 weeks of safety follow-up. During the active treatment period, two patients developed transient increase in serum creatinine, both of which were unrelated to MK-7 administration and were attributed to prerenal acute kidney injury associated with acute decompensation of chronic heart failure (cardiorenal syndrome type 1) in one patient and acute infectious gastroenteritis in another. Of note, the increase in creatinine in both patients was reversed when the primary injury was resolved. Other TEAEs included mild transient gastrointestinal symptoms, namely nausea, vomiting, diarrhea, and constipation, in nine (15%) patients, as well as self-resolving unilateral leg pain in one (2%) patient. There were no adverse events reported during the 2-week safety follow-up period.

Discussion

Among renal transplant recipients, 8 weeks of MK-7 supplementation was associated with significant improvement in arterial stiffness and 24-hour peripheral and central pressures. The mean reduction in cfPWV was 1.4 m/s, which was well beyond the reduction of 1 m/s recommended for a clinically relevant vascular effect.[23] In addition, MK-7 supplementation was associated with reduction in dp-ucMGP concentrations, and a positive correlation was present between the reduction in arterial stiffness, a surrogate of early CV disease, and the circulating concentration of dp-ucMGP, a marker of subclinical vascular vitamin K deficiency and calcification.[25–28] Of note, this association was independent of major confounders, including blood pressure changes or alteration in concomitant medications. The findings from this trial support the hypothesis that subclinical vitamin K deficiency may be a modifiable CV risk factor and may improve with MK-7 supplementation. Given that supplementation was associated with an improvement in arterial stiffness, this is also hypothesis generating that MK-7 supplementation may be an important future target for improvement in CV outcomes among renal transplant recipients.

Interestingly, the significant association between the administration of MK-7 and improvement in arterial stiffness was not mirrored by improvement in 24-hour augmentation index. Of note, however, augmentation index has only indirectly been associated with cfPWV and arterial stiffness and is not usually regarded as an index or surrogate of arterial stiffness. Physiologically, augmentation index is the index of pressure wave reflections that are modulated by changes in heart rate, vasodilation, and shifts in wave reflection coefficients.[24,25,29,30] This is not the first study to show a dissociation between PWV and augmentation index as markers of arterial stiffness, which supports the understanding that augmentation index is not a simple surrogate marker of arterial stiffness but is determined by other parameters such as reflection waves and heart rate.[25]

In prior observational studies, the prevalence of subclinical vitamin K deficiency has been reported to be as high as 80% in the renal transplant population, and dietary intake of vitamin K is thought to be insufficient for adequate MGP carboxylation.[16,17] In KING, subclinical vitamin K deficiency was present in more than half of all enrolled patients, and MK-7 supplementation significantly reduced the proportion of patients with vitamin K deficiency by approximately 75% (from 53.3% to 13.3%). Given that patients with baseline vitamin K deficiency had a more pronounced reduction in dp-ucMGP concentration and had the strongest association between improvement in dp-ucMGP and cfPWV, a targeted risk modification strategy with MK-7 supplementation is plausible.

The exact mechanism by which vitamin K2 supplementation improves indices of arterial stiffness is not fully understood. In a prior animal study, induced arterial calcification in rats and the consequent decreased arterial distensibility were reversed with high vitamin K intake over a period of 6 weeks.[31] Albeit observed in rats, this rapid decalcification effect of MK-7 has not been confirmed in humans. Small studies have demonstrated that supplementation may aid in slowing the progression of calcification. Although vitamin K supplementation among healthy adults and patients with ESRD has previously been associated with reduced concentrations of dp-ucMGP, a surrogate of vascular calcification, the true mechanism by which vitamin K supplementation improves vascular stiffness in humans and whether this improvement is directly related to arterial calcification, per se, has not been studied.[14,15,32] In fact, chronic kidney disease population is very special in many aspects; first, both traditional and population-specific factors (such as

Table 2
Changes in clinical, laboratory, and outcome measures of arterial stiffness and vitamin K status from baseline pre-vitamin K2 supplementation to follow-up post-vitamin K2 supplementation

Measures (N = 56*)	Baseline Pre-Vitamin K2 Supplementation (Mean ± SD)	Follow-up Post-Vitamin K2 Supplementation (Mean ± SD)	*P*-Value
Clinical and laboratory measures			
Body mass index (kg/m^2)	25.8 ± 4.8	26.0 ± 4.7	.36
Hemoglobin (g/dL)	12.8 ± 1.7	12.7 ± 1.8	.09
White blood count (×10^3/μL)	7.6 ± 2.4	7.5 ± 2.5	.59
Platelet count (×10^9/L)	247.5 ± 78.2	250.7 ± 79.7	.52
Serum albumin (mg/dL)	4.2 ± 0.3	4.1 ± 0.3	.003
Serum ALT (mg/dL)	27.2 ± 9.4	29.2 ± 8.3	.12
Serum uric acid (mg/dL)	6.4 ± 1.4	6.5 ± 1.6	.56
Serum creatinine (mg/dL)	1.3 ± 0.6	1.4 ± 0.7	.05
Serum calcium–phosphorus product (mg^2/dL^2)	37.0 ± 6.3	37.0 ± 7.1	.9
Serum parathyroid hormone (pg/mL)	96.0 ± 71.2	96.5 ± 105.5	.9
Serum vitamin D (pmol/L)	26.3 ± 11.4	25.8 ± 11.2	.61
Outcome measures			
cfPWV (m/s) (N = 56)	9.8 ± 2.2	8.4 ± 1.5	<.001
24-hour heart rate (beat/min) (N = 51)	75.7 ± 8.9	75.4 ± 9.4	.74
24-hour MAP (mm Hg) (N = 51)	100.8 ± 9.9	98.5 ± 8.8	.01
24-hour brachial (peripheral) SBP (mm Hg) (N = 51)	125.4 ± 11.8	123.0 ± 12.0	.048
24-hour brachial (peripheral) DBP (mm Hg) (N = 51)	80.0 ± 10.2	77.8 ± 8.0	.005
24-hour aortic (central) SBP (mm Hg) (N = 51)	127.0 ± 13.0	125.4 ± 13.5	.18
24-hour augmentation index (N = 51)	24.3 ± 7.9	25.2 ± 17.5	.70
dp-ucMGP (pmol/L) (N = 60)	556.1 ± 336.9	249.7 ± 161.8	<.001

ALT, alanine aminotransferase; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; dp-ucMGP, dephosphorylated-uncarboxylated matrix Gla protein; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation.

* N for clinical and laboratory measures and N for cfPWV reported for all patients included in the primary analysis population, defined as all patients with both baseline and follow-up cfPWV measures. N for 24-hour central blood pressure, augmentation index, and dp-ucMGP reported for all patients with both baseline and follow-up measures for each outcome. Patients with no available pre- and post-measurement for any test were excluded from the mean calculation and *P*-value for that test. *P*-value generated using paired *t*-test.

arterial calcifications and stiffening) modulate CV risk; dietary intake is overall limited; and the type of renal replacement therapy (dialysis vs. transplantation) adds another challenge to the understanding of CV risk determinants.[33–37] Mechanisms involved in arterial stiffness changes fall into two categories: passive and active.[38] Passive mechanisms depend on heart rate and elastic recoil of arterial wall fibers, and they are associated with rapid fluctuations in stiffness. Active mechanisms, on the other hand, involve both structural and dynamic components that are related to smooth muscle tone, turnover in the extracellular matrix, endothelial function, inflammation, and oxidative stress.[38,39] Structural changes of the arterial wall involving collagen and elastic fibers (such as occurs with aging) and the extracellular matrix (calcification for example) are time dependent, and their reversal, whenever possible, requires substantial time before it translates into functional amelioration (such as improvement in PWV). On the other hand, dynamic changes (eg, blood pressure changes) can occur more acutely, which determines fast changes in stiffness level. In our study, cfPWV improved over 8 weeks of MK-7 supplementation, and MAP and peripheral diastolic blood pressure decreased, while heart rate and augmentation index remained unchanged. Furthermore, arterial stiffness changes were only partially explained by blood pressure changes. This fast improvement in vascular wall function cannot be attributed to a structural change in the arterial wall related to MK-7 supplementation

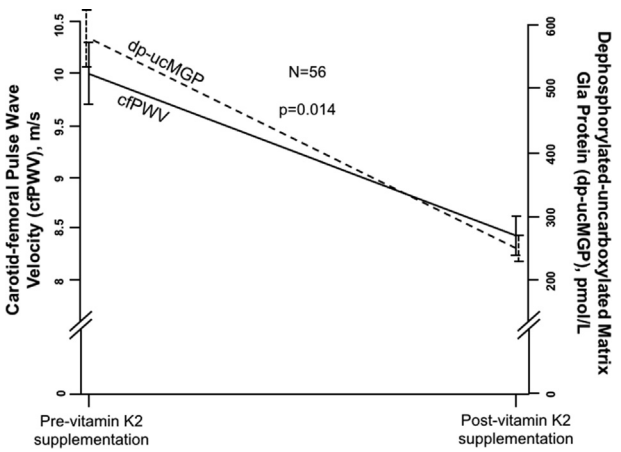

Figure 3. Association between carotid-femoral pulse wave velocity and dephosphorylated-uncarboxylated matrix Gla protein pre- and post-vitamin K2.

Table 3
Multivariate model demonstrating the independent association between the change in cfPWV and the change in dp-ucMGP in the primary analysis population

Association Between Δ cfPWV and Clinical Variables			
$R^2 = 0.19$, N = 56			
Variable (Increase by 10 Units)	Coefficient (95% CI)	Standard Error	*P*-Value
Δ dp-ucMGP (pmol/L)	0.03 (0.01 to 0.05)	0.01	.014
Age (y)	−0.1 (−0.5 to 0.3)	0.2	.75
Transplant duration (y)	0.8 (−0.01 to 1.7)	0.4	.053
Hemodialysis duration (mo)	0.1 (0.01 to 0.2)	0.05	.03
Δ 24-h MAP (mm Hg)	−0.03 (−0.6 to 0.5)	0.3	.9

cfPWV, carotid-femoral pulse wave velocity; CI, confidence interval; dp-ucMGP, dephosphorylated-uncarboxylated matrix Gla protein; MAP, mean arterial pressure; Δ, change.

(decalcifying effect). Instead, we postulate that dynamic active mechanisms have occurred in relation to the intervention involving, in addition to positive blood pressure changes, effects on endothelial function and inflammation, as demonstrated in other studies where vitamin K was also involved in cell-signaling pathways and regulation of gene expressions in vascular smooth muscle cells, suppression of interleukin-6 and other inflammatory cytokines, and improvement in arterial elasticity.[40,41]

This trial is limited by its single-arm, single-center design and the small sample size. CV outcomes were not investigated in the study, and all hypotheses related to improvement in CV outcomes were derived from the improvement in arterial stiffness, a surrogate end point. The cutoff value of dp-ucMGP to define vascular vitamin K deficiency may not necessarily reflect true physiological vitamin K deficiency. However, this value was consistent with prior studies given that to date, there is no consensus on the cutoff dp-ucMGP concentration to diagnose vitamin K deficiency. Furthermore, inflammatory mediators and endothelial function were not explored to support our suggestion about their role in mediating arterial stiffness change. The study was adequately powered to demonstrate a difference in cfPWV from baseline through 8 weeks but was underpowered to conclusively detect differences in subgroups of patients. Accordingly, the subgroup analyses should be considered exploratory and require further validation. Nonetheless, the results from this study serve as an important addition to adequately explore the association between subclinical vitamin K deficiency and CV outcomes among the renal transplant population in an adequately powered, large-sized randomized clinical trial.

Conclusions

This pilot, single-arm trial demonstrated that subclinical vitamin K deficiency is prevalent among renal transplant recipients. Additionally, MK-7 supplementation for 8 weeks is safe and is associated with significant improvement in both vitamin K status and measures of arterial stiffness, namely cfPWV, independently from 24-hour peripheral and central pressures as well as from other major confounders. Whether continued MK-7 supplementation confers sustained cfPWV and blood pressure improvement that translates into better CV outcomes in the renal transplant population warrants further investigation in a large-scale randomized clinical trial.

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The trial design and data collection were performed solely by the authors. All data analyses and manuscript drafting, including the final version, were performed by the authors, who take full responsibility for its final content and the decision to submit the report for publication.

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