Balkan Med J 2021;38:116-120

The evaluation of vitamin K status in children with febrile seizure

Kürşat Bora Carman[1], Yasemin Karal[2], Gül Gülen Mert[3], Arzu Ekici[4], Peren Perk[5], Coşkun Yarar[1], Çağatay Nuhoğlu[6], Gürkan Bozan[7], Ömer Kılıç[7], Meltem Dinleyici[7], Sabiha Şahin[7], Emrah Atay[8], Uğur Tokdemir[7], Baver Demir[5], Ener Çağrı Dinleyici[7], Dinleyici EC EFES Study Group

[1]Department of Pediatric Neurology, Eskisehir Osmangazi University School of Medicine, Eskişehir, Turkey
[2]Department of Pediatrics, Trakya University School of Medicine, Edirne, Turkey
[3]Department of Pediatric Neurology, Çukurova University School of Medicine, Adana, Turkey
[4]Clinic of Pediatric Neurology, Yüksek İhtisas Hospital, Bursa, Turkey
[5]Gaziantep Children's Hospital, Gaziantep, Turkey
[6]Department of Pediatrics, Haydarpaşa Numune Eduction and Training Hospital, İstanbul, Turkey
[7]Department of Pediatrics, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
[8]Department of Public Health, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey

Background: Febrile seizure is the most common neurological disorder in childhood. The exact pathophysiology of febrile seizures is unknown. Recent studies showed the role of vitamin K in nonhematological and inflammatory disorders. This study aimed to investigate the serum vitamin K levels in children with febrile seizures.

Aims: To evaluate vitamin K levels in children with febrile seizures.

Study Design: Prospective case-control study.

Methods: This multicenter study examined representative populations in 8 different cities in Turkey between April 1, 2018 and April 1, 2019. Blood samples were taken from all children at presentation. Vitamin K1, vitamin K2, tumor necrosis factor-alpha, interleukin 1 beta, and interleukin 6 levels were determined by enzyme-linked immunosorbent assay.

Results: A total of 155 children were included in the study—84 children with febrile seizures and 71 children in febrile control group. Serum vitamin K1 and vitamin K2 levels were also higher in children with febrile seizures than in the controls. The results of statistical analysis showed that vitamin K1 and vitamin K2 levels were correlated with tumor necrosis factor-alpha, interleukin 1 beta, and interleukin 6 levels. The median vitamin K1 and vitamin K2 levels of children experiencing their first febrile seizure were higher than those in children with recurrent febrile seizures. Type of febrile seizure has no effect on serum vitamin K1 and vitamin K2 levels.

Conclusion: In children with febrile seizures, vitamin K levels are higher than those in the control group. These new findings may contribute to elucidating the etiopathogenesis of febrile seizures.

The precise pathophysiology of febrile seizure (FS) is uncertain. Clinical and experimental studies showed that genetics, inflammation, and cytokines are involved. The most searched cytokines include interleukin (IL)-6), IL-1b, and tumor necrosis factor-alpha (TNF- α).[1-4]

The 2 natural sources of vitamin K are phylloquinone (vitamin K1) and menaquinone (MK) (vitamin K2). Vitamin K1, synthesized in plants, is the main source of dietary vitamin K in the western world. Vitamin K2 is derived mainly from intestinal microbiota and fermented food.[5] On the basis of the variations in the side-chain structure, vitamin K2 divides into a sequence of chemically related compounds called MKs.[5-7] It serves as a cofactor in vitamin K-dependent proteins for the enzymatic modification of glutamic acid residues into γ-carboxyglutamic acid through vitamin K-dependent γ-glutamyl carboxylase.[6-8]

Vitamin K has important biological actions, including those in the synthesis of several blood coagulation factors and in connection to bone metabolism and vascular changes. Recent studies showed that vitamin K levels were found to be related to inflammation.[5,9-12] The process of carboxylase is present in nearly all mammalian tissues, and 2 vitamin K-dependent proteins (VKDPs) have been found in the brain (Gas6 and protein S). Gas6 has been demonstrated to encourage brain cell survival and protect them from TNF-α-induced injury.[13,14] Results from a research by Reddi et al.[9] showed that the status of vitamin K in humans is inversely correlated with the levels of inflammatory markers that circulate. The role of vitamin K

Address for Correspondence: Kürşat Bora Carman, Department of Pediatric Neurology, Eskisehir Osmangazi University School of Medicine, Eskişehir, Turkey
e-mail: kbcarman@gmail.com

Received: May 16, 2020 Accepted: October 6, 2020, Available Online Date: February 26, 2021 • DOI:10.4274/balkanmedj.galenos.2020.2020.5.70

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: K.B.C. 0000-0002-4629-1873; Y.K. 0000-0003-0096-6676; G.G.M.0000-0002-1160-5617; A.E. 0000-0002-0813-7189; P.P. 0000-0002-0778-056x; C.Y. 0000-0001-7462-4578; Ç.N. 0000-0003-2187-4121; G.B. 0000-0001-5041-8892; Ö.K. 0000-0003-0168-4080; M.D. 0000-0002-8353-6796; S.Ş. 0000-0002-0655-4536; E.A. 0000-0002-6581-8626; U.T. 0000-0002-8500-4304; B.D. 0000-0002-8862-6790; E.Ç.D. 0000-0002-0339-0134.

Cite this article as:
Carman KB, Karal Y, Gülen Mert G, et al. The evaluation of vitamin K status in children with febrile seizure. *Balkan Med J*. 2021;38(2):116-120.

has been rarely researched in neurological diseases[15,16] and there are no previous studies on the presence of seizures. In this study, we aimed to investigate serum vitamin K levels in children with FS and compare them with their roles in febrile controls.

MATERIAL AND METHODS

Patient information

This prospective multicenter research was conducted between April 1, 2018 and April 1, 2019 in 8 different cities. The study was approved by a local ethical committee and supported by a university research grant. Documented written consent had been received from the parents of all the children.

Previous medical history and demographical characteristics of all children have been recorded. The use of antibiotics was recorded within the last 15 days. Detailed physical examinations, including neurological examinations, were performed.

The control group included age-matched children who were diagnosed with febrile disease but who did not have seizures and had no known history of previous FSs.

Laboratory analysis

Blood samples (3 cm^3) were collected in a serum separation tube from the seizure within 1 hour. The serum was immediately centrifuged and stored at –80°C. Vitamin K1, Vitamin K 2, TNF-α, IL-1β, and IL-6 levels were analyzed using an enzyme-linked immunosorbent assay (ELISA) kit, which is available commercially. The experiments were carried out on the instructions of the manufacturer (ELISA Assay Kits, BioTek, Winooski, VT, USA). To improve accuracy, all samples were measured in duplicate.

Statistical analysis

The levels of Vitamin K1, K2, TNF-α, IL-1β, and IL-6 are presented in the descriptive statistics tables as mean, median, standard deviation, and minimum and maximum values. Owing to the nonparametric distribution of these parameters, Mann-Whitney U and Kruskal-Wallis analyses were conducted to compare the medians of these parameters between the patients with FSs and controls. Analysis of correlation was conducted with Spearman correlation analysis, and multivariate logistic regression analysis was performed. The Statistical Package for the Social Sciences for windows 15.0 (SPSS Inc.; Chicago, IL, USA) was used for all analyses, and analysis was considered significant if $P < 0.05$.

TABLE 1. Demographic and Clinical Findings of the Study Group

	Patients with febrile seizures n (%)	Control group n (%)	*P*
Age, months, mean ±SD			
Age (min-max)	25.59±14.58 (3-60)	36.36±20.33 (6-60)	0.156
Gender (male/female)	51/33	45/26	0.431
Source of fever			
Upper respiratory tract infections	60 (71.4)	37 (52.1)	
Lower respiratory tract infections	8 (9.5)	19 (26.8)	
Acute gastroenteritis	10 (11.9)	14 (19.7)	
Other infections	6 (7.2)	1 (1.4)	

max, maximum; min, minimum; SD, standard deviation.

RESULTS

Patient characteristics

The study was conducted with 155 children: 84 children with FS (51 male and 33 female) and 71 children (45 male and 26 female) in the febrile control group. Sex distributions were similar between the group with FS and the control group ($P = 0.431$). The mean age of the group with FS was 25.59 ± 14.58 (minimum-maximum value of 3-60) months, and the mean age of the febrile control group was 36.36 ± 20.33 (minimum-maximum value of 6-60) months ($P = 0.156$). Laboratory features, including white blood cell counts, prothrombin time (PT), and activated partial thromboplastin time (aPTT), were similar.

Furthermore, 49 children (58.3%) experienced their first FS episode, and the median age of the recurrent group was higher than that of others. In the study group, 71.4% of seizures (60 of 84) were classified as simple FS. Positive family history for FS was present in 52.4% of children (44 of 84), and no correlation was determined between positive family history and the number of FS experienced. Demographic and clinical features are summarized in Table 1.

Laboratory analysis

Serum vitamin K1, vitamin K2, IL-1β, TNF-α, and IL-6 levels in the group with FS were all higher than those in the control group ($P < 0.001$ for all) (Table 2). In children with first FS, the median

TABLE 2. Serum Vitamin K1 and Vitamin K2 Levels in Patients with Febrile Seizure and Control Group

Laboratory parameters	Patients with febrile seizures (n = 84)	Control group (n = 71)	*P*
Vitamin K1 (ng/mL)			
Median (min-max)	11.1 (0.85-25.9)	3.36 (0.19-19.9)	<0.001*
Mean (SD)	11.67 (7.4)	6.03 (5.55)	
Vitamin K2 (ng/mL)			
Median (min-max)	659 (34-1403)	244 (1.77- 1295)	<0.001*
Mean (SD)	675.6 (418.6)	419.6 (371.6)	
TNF-α (ng/mL)			
Median (min-max)	512.95 (31.9-1322.2)	212.6 (39.3- 1065.0)	<0.001*
Mean (SD)	618.9 (401.9)	332.7 (284.6)	
IL-1β (pg/L)			
Median (min-max)	4426.6 (280.8-8568.3)	1776.7 (221.5- 7817.4)	<0.001*
Mean (SD)	4658 (2732)	2706 (2198)	
IL-6 (ng/mL)			
Median (min-max)	314.1 (13.6-80.8)	123.1 (21.4- 610.7)	<0.001*
Mean (SD)	368.1 (242.9)	214.9 (176.9)	

* P values are calculated by Mann-Whitney U test because of distribution of the parameter is nonparametric.
IL, interleukin; max, maximum; min, minimum; SD, standard deviation; TNF-α, tumor necrosis factor-alpha.

TABLE 3. Serum Vitamin K1, Vitamin K2, TNF-α, IL-1β, and IL-6 Levels Between the Patients Who Had First seizure and Those Who Had Recurrent Seizure

Laboratory parameters	First seizure (n = 49)	Recurrent seizure (n = 35)	*P*1	Control (n = 71)	*P*2	*P*3
Vitamin K1 (ug/mL)						
Median (min-max)	14.1 (0.85-25.9)	6.9 (1.5-23.7)	0.025	3.36 (0.19-19.9)	*P*2 < 0.001	*P*3 = 0.01
Mean (SD)	13.32 (7.8)	9.36 (6.3)		6.03 (5.55)		
Vitamin K2 (ng/mL)						
Median (min-max)	814.8 (34-1,403)	446 (83-1,283)	0.034	244 (1.77-1,295)	*P*2 < 0.001	*P*3 = 0.032
Mean (SD)	758.02 (422.8)	560.30 (389.8)		419.6 (371.6)		
TNF-α (ng/mL)						
Median (min-max)	855.9 (31.9-1,322.2)	364.5 (48.7-1,178.6)	0.012	212.6 (39.3-1,065.0)	*P*2 < 0.001	*P*3 < 0.018
Mean (SD)	719.5 (413.6)	478.1 (343.1)		332.7 (284.6)		
IL-1β (pg/L)						
Median (min-max)	6,183.8 (280-8,568)	3,611.8 (489.5-8,378)	0.029	1,776.7 (221.5-7,817.4)	*P*2 < 0.001	*P*3 < 0.010
Mean (SD)	5,209 (2,778)	3,886 (82,504)		2706 (2198)		
IL-6 (ng/mL)						
Median (min-max)	403.4 (13.6-880.8)	259.7 (42.2-799.1)	0.053	123.1 (21.4-610.7)	*P*2 < 0.001	*P*3 < 0.020
Mean (SD)	417.4 (258.8)	299 (202.6)		214.9 (176.9)		

*P values are calculated by Mann-Whitney U test because of distribution of the parameter is nonparametric.
p1, first seizure versus recurrent seizure; p2, first seizure versus control; p3, recurrent seizure versus control.
IL, interleukin; max, maximum; min, minimum; SD, standard deviation; TNF-α, tumor necrosis factor-alpha.

TABLE 4. Multivariate Logistic Regression Results of the Study Parameters

			95% CI for Exp(B)		
Variables	B	Exp(B)*	Lower	Upper	*P*
Age	-0.027	0.974	0.953	0.995	0.016
Positive family of FS	1.644	5.178	1.975	13.573	0.001
Positive family of epilepsy	0.190	1.209	0.280	5.227	0.799
Vitamin K1 level	0.276	1.318	1.020	1.703	0.034
Vitamin K2 level	-0.005	0.996	0.991	1.000	0.031
TNF-α	0.002	1.002	0.997	1.007	0.551
IL-1β	0.000	1.000	1.000	1.001	0.359
IL-6	-0.002	0.998	0.989	1.006	0.588
Constant	-0.322	0.725	–	–	0.522

*Odds ratio.
CI, confidence interval; FS, febrile seizure; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

vitamin K1 and vitamin K2 levels were higher than those in children with recurrent FS ($P = 0.025$ for vitamin K1 and $P = 0.034$ for vitamin K2). Serum TNF-α and IL-1β levels in the group with first seizure were all higher than the levels in those with recurrent seizure ($P = 0.012$ and $P = 0.029$), whereas serum IL-6 levels were similar between the 2 groups ($P = 0.053$) (Table 3). Serum vitamin K1, vitamin K2, TNF-α, IL-1β, and IL-6 levels in the group with first seizure and those with recurrent seizure were all higher than the level in the control group (Table 3). Type of FS has no influence on the levels of both vitamin K1 and vitamin K2 ($P > 0.05$). There was no significant correlation between both vitamin K1 and vitamin K2 levels and the patient's age, PT, aPTT, antibiotic usage within the previous 15 days, and the final diagnosis of patients.

In this study, vitamin K1 and vitamin K2 levels were positively correlated (r = 0.933, $P < 0.001$). In addition, detailed statistical analysis showed that both vitamin K1 and vitamin K2 levels were independently associated with the levels of TNF-α, IL-1β, and IL-6 levels (r = 0.973, $P < 0.001$ and r = 0.926, $P < 0.001$; r = 0.935, $P < 0.001$ and r = 0.912, $P < 0.001$; and r = 0.925, $P < 0.001$ and r = 0.899, $P < 0.001$).

Multivariate logistic regression analysis was performed to determine the effect of some related factors (independent variables) on the dependent variable. According to the results, age, family history, FS, vitamin K1, and vitamin K2 variables were found significant with the binary logistic regression analysis by controlling other variables. An increase in age and vitamin K2 levels decrease

the probability of FS. On the contrary, positive family history and an increase in vitamin K1 levels increase the probability of being a patient. The results are presented in Table 4.

DISCUSSION

In this study, the results showed higher serum vitamin K1 and vitamin K2 levels in children with FS than in febrile children without FS. Vitamin K is a cofactor of carboxylation of VKDPs in the brain. Gas6 is expressed in the cerebral, piriform cortex; hippocampus; thalamic and hypothalamic structures; and midbrain in adult rats.[17-19] Different researches demonstrated that Gas6 has functions in cell growth, chemotaxis, survival, mitogenesis, and myelination.[13,14]

Prieto et al.[20] reported a decline in the expression of Gas6 with age in a tissue-specific manner, and the reduction was most prominent in the frontal cortex, with the levels in rats aged 24 months being > 84% lower than those in rats aged 6 months. However, in the hippocampus striatum, these ratios were > 50%.[21] These age-dependent changes in vitamin K level might have a role in the pathogenesis of FS, which occurs in a specific age period.

Vitamin K1 is of plant origin. It is rich in green tea, bean, olive, and leafy green vegetables such as broccoli and spinach, whereas vitamin K2 has a bacterial origin and is synthesized by *Bacteroides, Veillonella*, and *Enterobacter*, which are the usual members of the intestinal microbiota.[15,16] Karl et al.[22] investigated the relationship between bacterially derived vitamin K levels and gut microbiota and reported that the relative abundance of *Bacteroides* and *Prevotella* were associated with MK forms. The development of gut microbiota begins at birth, and its stability is achieved during adulthood. The colonization and expansion of gut bacteria are dominated by *Actinobacteria* and *Proteobacteria*, which shift toward the one dominated by *Bacteroidetes and Firmicutes*.[16] The time of this process coincides with the time of FS occurrence. FS occurs in children aged < 5 years, with peaks in those aged 12-18 months.[1-4] It might be speculated that intestinal dysbiosis might be involved in the pathogenesis of FS.

Inflammation and cytokines play a crucial role in the pathogenesis of FS.[4] Evidence indicates that vitamin K has anti-inflammatory activity and that this effect is mediated by cytokines, and vitamin K status in humans has been reported to be inversely correlated with circulating inflammatory marker levels.[9,10]

The findings of an animal study showed that vitamin K decreases rotenone-induced TNF-α, IL-1β, and IL-6 production.[23,24] In addition, Grommes et al.[25] reported reduced expression of proinflammatory cytokines in Gas6-treated cells. In contrast to these reports, the results of this study showed a positive correlation between vitamin K levels and proinflammatory markers (TNF-α, IL-1β, and IL-6). The increased expression of vitamin K might be an answer to proinflammatory cytokines.

Our study has some limitations. The healthy, nonfebrile children were not taken as a control group. This point might be an important challenge in this study. Synthetic short-chain vitamin K1 is widely used in food supplements, and some foods might contain bacteria-derived MKs, such as salami, cheese, and milk.[26,27] A study conducted with healthy volunteers also showed that circulating vitamin Ks were plotted as a time function. The peak values for both vitamin Ks were seen at about 4 hours after mealtime, followed by a rapid decline. Vitamin K returned to near baseline concentrations at 8 hours after mealtime.[26] Blood samples were collected within 1 hour after seizure in this study. The feeding habits of the participants and the last time the patients ate food were not questioned in this study. This point might be considered the second limitation of this study. Although this is a pilot study, we could not perform a power analysis at the beginning of the study. Regarding post-hoc analysis, our preliminary results on vitamin K1 and K2 levels showed the power of this study to be 99% and 97%, respectively.

In conclusion, this study shows that vitamin K levels in children with FS are higher than those in the control group. To the best of our knowledge, this study is the first to report the roles of vitamin K in FS. These new findings may contribute to clarifying the pathogenesis of FS.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Eskişehir Osmangazi University (No:2016/80558721-82).

Patient Consent for Publication: Written consent has been received from the parents of all the children.

Data-sharing Statement: N/A.

Acknowledgment: The authors thanks Samet ECE from Diagen Laboratories Ltd, Ankara, Turkey, for their kind support during laboratory analysis.

Author Contributions: Concept - K.B.C., E.C.D.; Design - K.B.C., Y.K., S.S., O.K.; Supervision - E.C.D., K.B.C.; Materials - K.B.C., G.B., M.D.; Data Collection and/or Processing - G.G.M., P.P., C.Y., A.E., C.N., S.S., U.T., B.D.; Analysis and/or Interpretation - E.A., E.C.D., K.B.C.; Literature Review - K.B.C.; Writing - K.B.C., E.C.D.; Critical Review - K.B.C., E.C.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: This study has been supported by a Eskişehir Osmangazi University Research Grant.

REFERENCES

1. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia.* 1993;34(4):592-596. [Crossref]
2. Waruiru C, Appleton R. Febrile seizures: an update. *Arch Dis Child.* 2004;89(8):751-756. [Crossref]
3. Kwon A, Kwak BO, Kim K, et al. Cytokine levels in febrile seizure patients: a systematic review and meta- analysis. *Seizure.* 2018;59:5-10. [Crossref]
4. Saghazadeh A, Gharedaghi M, Meysamie A, Bauer S, Rezaei N. Proinflammatory and anti-inflammatory cytokines in febrile seizures and epilepsy: systematic review and meta-analysis. *Rev Neurosci.* 2014;25(2):281-305. [Crossref]
5. Fusaro M, Gallieni M, Rizzo MA, et al. Vitamin K plasma levels determination in human health. *Clin Chem Lab Med.* 2017;55(6):789-799. [Crossref]
6. Vermer C, De Boer-Van den Berg MA. Vitamin K -dependent carboxylase. Haematologia (Budap) 195;18:71.
7. Shearer MJ, Newman P. Recent trends in the metabolism and cell biology of vitamin K with special reference to vitamin K cycling and MK-4 biosynthesis. *J Lipid Res.* 2014;55(3):345-362. [Crossref]
8. Beulens JWJ, Booth SL, van den Heuvel EGHM, Stoecklin E, Baka A, Vermeer C. The role of menaquinones (vitamin K_2) in human health. *Br J Nutr.* 2013;110(8):1357-1368. [Crossref]
9. Reddi K, Henderson B, Meghji S, et al. Interleukin 6 production by lipopolysaccharide-stimulated human fibroblasts is potently inhibited by naphthoquinone (vitamin K) compounds. *Cytokine.* 1995;7(3): 287-290. [Crossref]

10. Shea MK, Booth SL, Massaro JM, et al. Vitamin K and vitamin D status: associations with inflammatory markers in the Framingham Offspring Study. *Am J Epidemiol.* 2008;167(3):313-320. [Crossref]
11. Booth SL. Roles for vitamin K beyond coagulation. *Annu Rev Nutr.* 2009;29:89-110. [Crossref]
12. Khojah HM, Ahmed S, Abdel-Rahman MS, Alkhalil KM, Hamza AB. Vitamin homologs as potential biomarkers for disease activity in patients with rheumatoid arthritis. *J Bone Miner Metab.* 2017;35(5):529-535. [Crossref]
13. Ferland G. Vitamin K, an emerging nutrient in brain function. *Biofactors.* 2012; 38(2):151-157. [Crossref]
14. Ferland G. Vitamin K and brain function. *Semin Thromb Hemost.* 2013;39(8):849-855. [Crossref]
15. Aydin S. Can vitamin K synthesis altered by dysbiosis of microbiota be blamed in the etiopathogenesis of venous thrombosis? *Biosci Microbiota Food Health.* 2017;36(3):73-74. [Crossref]
16. Ihekweazu FD, Versalovic J. Development of the Pediatric Gut Microbiome: Impact on health and disease. *Am J Med Sci.* 2018;356(5):413-423. [Crossref]
17. Popescu DC, Huang H, Singhal NK, et al. Vitamin K enhances the production of brain sulfatides during remyelination. *PLoS One.* 2018;13(8):e0203057. [Crossref]
18. Lasemi R, Kundi M, Moghadam NB, Moshammer H, Hainfellner JA. Vitamin K2 in multiple sclerosis patients. *Wien Klin Wochenschr.* 2018;130(9-10):307-313. [Crossref]
19. Ferland G. Vitamin K and the nervous system: an overview of its actions. *Adv Nutr.* 2012;3(2): 204-212. [Crossref]
20. Prieto AL, Weber JL, Tracy S, Heeb MJ, Lai C. Gas6, a ligand for the receptor protein-tyrosine kinase Tyro-3, is widely expressed in the central nervous system. *Brain Res.* 1999;816(2):646-661. [Crossref]
21. Tsaioun KI, Denisova NA, Obin M, Joseph J. Novel groth factor Gas6, phosphatidylserine and their age-related changes in the rat brain. *Neurosci Res Commun.* 2000;26(2):113-122. [Crossref]
22. Karl JP, Meydani M, Barnett JB, et al. Fecal concentrations of bacterially derived vitamin K forms are associated with gut microbiota composition but not plasma or fecal cytokine concentrations in healthy adults. *Am J Clin Nutr.* 2017;106(4):1052-1061. [Crossref]
23. Yu YX, Li YP, Gao F, et al. Vitamin K2 suppresses rotenone-induced microglial activation in vitro. *Acta Pharmacol Sin.* 2016;37(9):1178-1189. [Crossref]
24. Pan MH, Maresz K, Lee PS, et al. Inhibition of TNF-α, IL-1α, and IL-1β by pretreatment of human monocyte-derived macrophages with menaquinone-7 and cell activation with TLR agonists In Vitro. *J Med Food.* 2016;19(7):663-669. [Crossref]
25. Grommes C, Lee CY, Wilkinson BL, et al. Regulation of microglial phagocytosis and inflammatory gene expression by Gas6 acting on the Axl/Mer family of tyrosine kinases. *J Neuroimmune Pharmacol.* 2008;3(2):130-140. [Crossref]
26. Schurgers LJ, Teunissen KJF, Hamulyák K, Knapen MHJ, Vik H, Vermeer C. Vitamin K-containing dietary supplements: comparison of synthetic vitamin K1 and natto-derived menaquinone-7. *Blood.* 2007;109(8):3279-3283. [Crossref]
27. Walther B, Karl JP, Booth SL, Boyaval P. Menaquinones, bacteria, and the food supply: the relevance of dairy and fermented food products to vitamin K requirements. *Adv Nutr.* 2013;4(4):463-473. [Crossref]