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ORIGINAL RESEARCH

Associations Between Vitamin K and Suicide Attempts in Patients with Depression: A Case-Control Study

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Background: Hypovitaminosis K has been linked to depression and suicide, but epidemiological research is scarce. This study aimed to explore the association among vitamin K with depression and suicidal attempts.

Methods: This was a retrospective cross-sectional study involving 146 cases with a history of suicidal attempts and 149 subjects without a lifetime history of suicidal attempts. The levels of thyroid hormones, lipid profile, inflammatory cytokines, and vitamins were measured.

Results: Subjects who had suicidal attempts presented with a significant decrease in FT4, TC, vitamin D, and vitamin K but increased CRP levels. In these variables, vitamin K has a better diagnostic value for suicidal attempts in depressed patients, with a sensitivity of 0.842 and a specificity of 0.715. Correlation analysis suggested that vitamin K was significantly and positively related to FT4, TC, LDL, and sdLDL. Multivariate analysis showed that serum vitamin K level predicts suicidal attempts in depressive patients (OR = 0.614, $P = 0.004$, 95% CI 0.153–0.904). Moreover, a negative correlation between vitamin K and suicidal attempts was also noted for partial FT4, CRP, and vitamin D strata analysis.

Conclusion: Our study suggests that low vitamin K levels were correlated with suicidal attempts in patients with depression, indicating that vitamin K deficiency might be a biological risk factor for depression.

Keywords: vitamin K, suicidal attempts, depression

Introduction

Depression, the second most important cause of disability globally, is characterized by low mood, reduced interest, and cognitive impairment.[1] Depression causes soaring costs for treatment and decreased productivity, especially suicidal attempts. The pathogenesis of depression has not yet been extensively established. Some investigations have revealed the underlying effect of new biological biomarkers which might impact mood, including endocrine metabolites.[2,3] Thus, exploring novel biomarkers for diagnosing diseases might have clinical implications.

A suicidal attempt is a common clinical manifestation for depressed patients, leading to physical damage, loss of life, and adverse societal psychosocial and economic effects.[4] Suicidal attempts emerge from a complex dynamic and unique interplay among biological, psychological, and social factors, making it challenging to identify who would attempt suicide.[5] Thus, the high prevalence of suicide attempts among cases with depression highlights the need to identify the underlying biomarkers associated with this condition.

The widespread association of vitamin K with cognitive decline and mental disorders[6] indicates that hypovitaminosis K may contribute to the pathogenesis and development of depression. Vitamin K is a unique cofactor to the γ-glutamyl carboxylase enzyme and participates in synthesizing sphingolipids, key membrane components involved in cognitive

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behavior and prevalent in brain tissue.[7] Moreover, the protective effect of vitamin K in maintaining cognitive integrity is thought to be mediated, in part, via its anti-inflammatory properties,[8] which may link vitamin K deficiency to depression.

Previous studies have reported that vitamin K deficiency was involved in hypoactivity and a lack of exploratory behavior in animal models, whereas its supplementation antagonized depression-like behaviors.[9,10] Epidemiological studies concerning the relationship between vitamin K and depression remain unclear and non-conclusive. For example, recent studies identified a positive association between vitamin K intake and depressive symptoms in late adulthood,[11,12] but there was also an observation with non-significant results in Spanish children.[13] Moreover, most clinical observations did not measure vitamin K levels in serum samples, while population-based investigations were more commonly investigated in the elderly population and measured depression generally via self-administered questionnaires instead of evaluating psychiatric diagnosis by a psychiatrist.[14]

This study explored the relationship between serum vitamin K levels and suicidal attempts in depressive patients well-characterized in terms of psychiatric diagnosis. Our investigation mainly aimed to compare the serum levels of vitamins, including vitamins A, D, E, and K, in depressive cases with or without suicidal attempts. We hypothesized that serum vitamin K levels would be lower in patients with suicidal attempts than in those without suicidal attempts and that hypovitaminosis K in depressive cases with suicidal attempts would be correlated with less favorable clinical characteristics and subsequent deterioration.

Materials and Methods

Study Population

Two hundred ninety-five patients with depression, according to Structured Clinical Interview for DSM-IV (SCID) criteria, were recruited in our study upon admission to the Renmin Hospital of Wuhan University from April 2021 to November 2022. Of those, 146 had recently presented a suicidal attempt, and 149 had no lifetime history of suicidal attempts. Suicidal attempts are "situations in which a person performs a life-threatening behavior with the intent of jeopardizing life or to give the appearance of such intent".[15] Sociodemographic data for these patients are shown in Table 1. All cases aged 18 to 65 years were on psychiatric medication for their current mood episode at the moment of sample collection. All subjects underwent a general physical examination to exclude infection. The participants treated with antibiotics and anti-inflammatory medications were excluded from our observation. All participants provided written informed consent, and our study was approved by the medical ethics review committee of Renmin Hospital of Wuhan University (WDRY2021-K041). We confirm that our study complies with the Declaration Helsinki.

Biochemical Measurements

All patients fasted overnight. Blood samples were drawn between 8 and 9 a.m. from the antecubital vein. The blood samples were centrifuged at 3000 rpm for 5 minutes, and the serum was collected to be stored at −80 °C until analysis. The levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), lipoprotein(a) (Lp(a)), C-reactive protein (CRP), and small dense low-density lipoprotein (sdLDL) were measured. Moreover, the levels of vitamins A, D, E, and K were detected by LC-MS/MS according to previously reported methods.[16,17]

Statistical Analysis

Categorical results were presented as numbers (percentages), and continuous data were shown as mean ± s.d. All data were analyzed by IBM SPSS version 20.0 statistics software (Chicago, IL, USA). Percentage data for categorical results and average values for continuous variables were compared using chi-squared and Mann–Whitney *U*-tests, respectively. Spearman correlation analysis assessed the associations between vitamins and thyroid hormones, lipid levels, and inflammatory response. Univariate and multivariate logical regression analysis was performed to analyze the associations between depressive risk factors and suicidal attempts. Multiple regression analysis was carried out to predict the biomarkers for suicidal attempts in depressed patients. ROC curve analysis was used to evaluate the diagnostic efficacy of FT4, TC, CRP, vitamin D, and vitamin K for suicidal attempts. Stratified analysis was performed to analyze further the associations among vitamin K and suicidal attempts in depressed patients after stratification by the length of illness, FT4, TC, CRP, and vitamin D. All testing was two-tailed, and $P< 0.05$ was regarded as statistical significance.

Table 1 Characteristics of Patients with or Without Suicide Attempts

Characteristics	Without Suicidal Attempts (n=149)	With Suicidal Attempts (n=146)	*P*
Socio-demographics			
Male/female	49/100	48/98	0.658
Age, years	35.77±16.25	30.67±15.43	0.399
Education level, years	10.48±5.24	10.59±4.16	0.846
Psychiatric disorder			
Length of illness, years	3.41±4.67	4.05±5.55	0.290
Current psychiatric medication			
Antidepressants (%)			
SSRI	35 (23.5)	17 (11.6)	0.031
Others	25 (16.8)	29 (19.9)	0.591
Lithium	38 (25.5)	33 (22.6)	0.705
Anticonvulsants	76 (51.0)	54 (37.0)	0.044
Antipsychotics			
Typical	69 (46.3)	75 (51.4)	0.634
Atypical	63 (42.3)	79 (54.1)	0.759
Vascular risk factors, n (%)			
Smoking	15 (10.07)	8 (5.48)	0.068
Alcohol consumption	38 (25.50)	29 (19.86)	0.307
Serum biomarkers			
FT3 (ng/L)	3.30±0.50	3.32±0.46	0.657
FT4 (ng/L)	1.27±0.28	1.02±0.33	<0.001
TSH (IU/L)	2.46±1.67	2.60±1.06	0.724
TC (mmol/L)	4.09±0.84	3.74±0.70	<0.001
TG (mmol/L)	1.24±0.68	1.42±0.90	0.061
HDL (mmol/L)	1.15±0.31	1.18±0.30	0.453
LDL (mmol/L)	2.42±0.80	2.25±0.68	0.051
sdLDL (mmol/L)	0.58±0.28	0.57±0.33	0.648
Lp (a) (mg/L)	212.65±245.90	171.74±197.26	0.129
CRP (mg/L)	1.17±3.72	3.30±2.74	0.002
Vitamin A (μmol/L)	1.32±0.46	1.31±0.41	0.879
Vitamin D (ng/mL)	16.50±7.27	12.73±5.57	<0.001
Vitamin E (μmol/L)	15.91±6.78	16.82±7.55	0.280
Vitamin K (ng/mL)	1.47±0.84	0.67±0.50	<0.001

Results

Comparison of General Data Among Subjects with and without Suicidal Attempts

A total of 295 subjects with depression were enrolled in our study. One hundred forty-nine cases presented a history of suicidal attempts, and 146 patients had no history of suicidal attempts in their lifetime. The characteristics of the samples are summarized in Table 1. There is no significant difference in average age [(35.77±16.25) vs (30.67±15.43)], education level, or gender distribution between cases without suicidal attempts and those with suicidal attempts. Additionally, there was no significant difference in length of illness, smoking, alcohol consumption, and the levels of FT3, TSH, TG, HDL, LDL, sdLDL, Lp(a), vitamin A, and vitamin E between the two groups. The frequencies of the types of psychiatric medication were similar among the two groups, except for the utilization of SSRI antidepressants and anticonvulsants, which were higher in cases with suicidal attempts than in those without suicidal attempts. Subjects with suicidal attempts had significantly lower levels of FT4, TC, vitamin D, and vitamin K and higher CRP levels than those without suicidal attempts (all $P < 0.05$).

Diagnostic Value of Vitamin K for Patients with Suicidal Attempts

As shown in Table 1, the levels of vitamin K in patients with suicidal attempts [(0.67±0.50) ng/mL] were significantly decreased compared with those without suicidal attempts [(1.47±0.84) ng/mL]. We further performed a ROC curve analysis to evaluate the diagnostic efficacy of FT4, TC, CRP, vitamin D, and vitamin K for suicidal attempts. As shown in Figure 1, the diagnostic value of vitamin K for suicidal attempts in depressive patients was higher than that of FT4, TC, CRP, and vitamin D, according to the AUC. Moreover, the results in Table 2 showed that the AUC of vitamin K was 0.813 (P = 0.000, 95% CI 0.763–0.863), with a sensitivity of 0.842 and specificity of 0.715, and the cut-off value of vitamin K was calculated as 2.000 ng/mL with a Youden index of 0.251.

Correlation Analysis Among Vitamins and Potential Suicide Markers in Cases with Depression

As shown in Table 3, vitamin A was significantly and positively associated with TC (r = 0.179, P = 0.003), TG (r = 0.335, P = 0.000), LDL (r = 0.214, P = 0.003), and sdLDL (r = 0.378, P = 0.000), but negatively correlated with HDL (r = −0.185, P = 0.002) and CRP (r = −0.140, P = 0.019). Vitamin E levels were found to be negatively correlated with FT3 (r = −0.144, P = 0.018) and FT4 (r = −0.138, P = 0.023), whereas they were positively associated with TC (r = 0.307, P = 0.000), TG (r = 0.248, P = 0.000), LDL (r = 0.216, P = 0.000), and sdLDL (r = 0.255, P = 0.000). Additionally, vitamin K levels were significantly and positively related to FT4 (r = 0.265, P = 0.000), TC (r = 0.147, P = 0.014), LDL (r = 0.117, P = 0.049), and sdLDL (r = 0.122, P = 0.041), suggesting vitamin K may affect thyroid function and lipid metabolism in depressed patients.

Logistic Regression Analysis of Suicidal Attempts in Depressive Patients

In order to investigate the predictors of suicidal attempts in depressed subjects, we entered whether cases with depression had suicidal attempts as the dependent variable and each risk factor as the independent variable into the regression model. Univariate analysis revealed that the length of illness, FT4, TSH, TC, HDL, vitamin D, and vitamin K levels were associated with suicidal attempts in patients with depression. Multivariate analysis indicated that serum FT4 (OR = 0.844, P = 0.011, 95% CI: 0.127–0.853), vitamin D (OR = 0.689, P = 0.013, 95% CI: 0.108–0.907), and vitamin K (OR = 0.614, P = 0.004, 95% CI: 0.153–0.904) abundances are the predictors for suicidal attempts in depressive patients (Table 4).

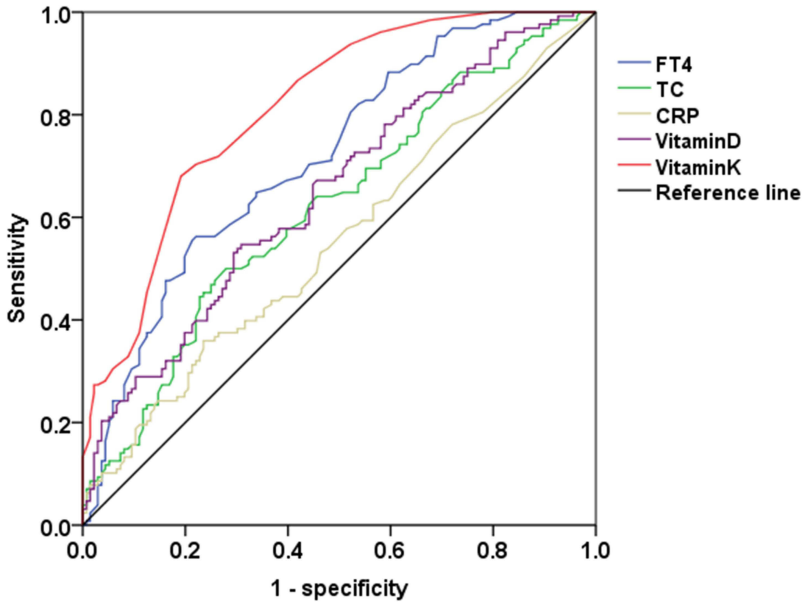

Figure 1 ROC curve analysis of risk factors in the diagnosis of suicidal attempts in depressive patients.

Table 2 The Diagnostic Value of Risk Factors for Suicidal Attempts Using ROC Curve Analysis

Variable	Sensitivity	1-specificity	Area	Youden Index	Cut-off value	*P*	95% CI
FT4	0.555	0.787	0.717	0.342	1.205	0.000	0.656–0.778
TC	0.477	0.743	0.621	0.220	4.075	0.001	0.553–0.688
CRP	0.359	0.765	0.551	0.124	0.830	0.156	0.481–0.620
Vitamin D	0.672	0.544	0.648	0.216	12.855	0.000	0.582–0.714
Vitamin K	0.842	0.715	0.813	0.251	2.000	0.000	0.763–0.863

Table 3 Correlation Among Vitamins with Thyroid Hormones, Lipid Levels, and Inflammatory Response

Variable	Vitamin A		Vitamin D		Vitamin E		Vitamin K	
	r	*P*	r	*P*	r	*P*	r	*P*
FT3	0.65	0.288	−0.020	0.747	−0.144	0.018	−0.106	0.081
FT4	−0.034	0.584	0.050	0.410	−0.138	0.023	0.265	0.000
TSH	0.039	0.522	−0.046	0.452	0.013	0.826	−0.025	0.686
TC	0.179	0.003	0.023	0.705	0.307	0.000	0.147	0.014
TG	0.335	0.000	0.003	0.965	0.248	0.000	0.008	0.896
HDL	−0.185	0.002	−0.018	0.766	0.103	0.083	−0.036	0.542
LDL	0.214	0.000	−0.003	0.965	0.216	0.000	0.117	0.049
sdLDL	0.378	0.000	0.036	0.547	0.255	0.000	0.122	0.041
Lp (a)	0.100	0.097	0.052	0.393	0.082	0.176	0.098	0.105
CRP	−0.140	0.019	0.072	0.231	−0.006	0.920	0.003	0.963

Note: Adjustment for antidepressants.

Table 4 Logistic Regression Analysis on Predictors of Suicide Attempt in Depressive Patients

Variable	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	0.326	0.019–1.028	0.307			
Length of illness	0.701	0.381–0.915	0.016	0.854	0.297–1.074	0.084
Education level	1.126	0.824–1.850	0.519			
FT3	1.023	0.852–1.924	0.349			
FT4	0.821	0.169–0.964	0.008	0.844	0.127–0.853	0.011
TSH	1.367	1.029–2.957	0.013	1.294	0.895–2.564	0.217
TC	0.522	0.164–0.897	0.007	0.517	0.219–1.066	0.153
TG	1.059	0.527–1.683	0.419			
HDL	0.529	0.047–0.866	0.024	0.563	0.086–1.104	0.057
LDL	0.668	0.155–1.153	0.512			
sdLDL	1.624	0.553–3.741	0.664			
Lp (a)	0.311	0.108–1.009	0.252			
CRP	3.025	0.994–5.667	0.064			
Vitamin A	1.604	0.847–3.367	0.186			
Vitamin D	0.712	0.119–0.976	0.009	0.689	0.108–0.907	0.013
Vitamin E	1.539	0.847–2.655	0.510			
Vitamin K	0.529	0.148–0.866	<0.001	0.614	0.153–0.904	0.004

Note: Adjustment for antidepressants.

Table 5 Multiple Regression Analysis for Biomarkers and Suicidal Attempts

Variable	Length of Illness	FT4	Vitamin D	Vitamin K
B-coefficient	0.095	0.081	−0.134	−0.325
P	0.106	0.228	0.076	<0.001

Note: Adjustment for antidepressants.

Table 6 Correlations of Vitamin K and Suicidal Attempts Across Categories of Length of Illness, FT4, TC, CRP, and Vitamin D

	β	T	P
Length of illness			
≥3	−0.175	−4.715	<0.001
<3	−0.131	−2.948	0.018
FT4			
≥1.14	−0.057	−0.814	0.315
<1.14	−0.163	−3.541	<0.001
TC			
≥3.91	−0.063	−0.077	0.532
<3.91	−0.094	−0.943	0.168
CRP			
≥2.22	−0.195	−1.557	0.016
<2.22	−0.084	−0.634	0.326
Vitamin D			
≥14.63	−0.042	−0.083	0.417
<14.63	−0.147	−2.461	0.024

Note: Adjustment for antidepressants.

Association Among Risk Factors and Suicidal Attempts in Depressive Patients

The relationships between risk factors (length of illness, FT4, vitamin D, and vitamin K) and suicidal attempts were further assessed by multivariate regression analysis. As shown in Table 5, vitamin K, but not length of illness, FT4, and vitamin D were significantly and negatively associated with suicidal attempts in depressed patients.

Association Among Vitamin K and Suicidal Attempts in Depressed Patients After Stratification by Risk Factors

Cases were stratified according to the length of illness, FT4, TC, CRP, and vitamin D. Next, we performed a linear regression analysis to assess the associations between $\log_{10}$-transformed vitamin K and suicidal attempts in patients with depression. Inverse associations between vitamin K and suicidal attempts were observed for all lengths of illness strata, while no associations were found in the TC strata. In addition, the negative correlations between vitamin K and suicidal attempts were noted for partial FT4, CRP, and vitamin D strata (Table 6).

Discussion

To the best of our knowledge, our study first reported that lower levels of vitamin K were correlated with an increased risk of suicidal attempts in depressed patients. Although the association between deficient vitamin D levels and suicidal ideation has been reported previously,[18] the effect size of vitamin K was more pronounced than that of vitamin D in patients with the most severe symptoms in our study. Clinically insufficient and deficient vitamin K levels were more likely to be found in cases with suicidal attempts.

It is well known that vitamin D has been increasingly associated with cognitive decline and mental health, and its deficiency may contribute to the development of depression.[19,20] Studies in humans demonstrated that vitamin D receptors (VDR) and 1α-hydroxylase had been found in brain tissue, which can catalyze the synthesis of 1,25-dihydroxy vitamin D (calcitriol, the bioactive form of vitamin D).[21,22] Moreover, vitamin D can protect the integrity of neurons and affect inflammatory pathways in the hippocampus and neocortex, which have been associated with depression.[23,24] In addition, epidemiological evidence concerning the negative association between vitamin D and depression has been confirmed.[20] In the present study, we also reported that subjects with suicidal attempts had significantly lower levels of vitamin D than those without suicidal attempts, suggesting that vitamin D is linked to the severity of depression. Similar to our findings, a recent study revealed a negative association between depression severity and vitamin D.[25] However, the predictive effect of vitamin D for suicidal attempts in depressive patients is lower than that of vitamin K by ROC curve analysis. Thus, our study mainly explored the correlations between serum vitamin K levels and suicidal attempts in depressed subjects.

The association between serum vitamin K and suicidal attempts in depressed patients has not been fully clarified. The reason may be that no reliable method exists to measure serum vitamin K levels. We can quantify vitamin K concentrations in serum samples using liquid chromatography-tandem mass spectrometry (LC-MS/MS).[17] Therefore, our study detected vitamin K levels in 295 patients with depression and analyzed their predictive value for suicidal attempts. Our observation confirms the previous paper, based mainly on serum samples with symptom reports but not vitamin K intake, by showing the association between vitamin K and suicidal attempts in a relatively large cohort. Remarkably, low serum levels of vitamin K were found in patients with suicidal attempts. Of course, previous studies have also reported that vitamin K intake is negatively and significantly correlated with depressive symptoms in overweight participants.[12,26] Although the possible mechanism of vitamin K in the development of depression has not been thoroughly demonstrated, the low-vitamin K diet was found to be linked to higher contents of ceramides, which contribute to the activation of pro-inflammatory pathways, the accumulation of reactive oxygen species (ROS), the repression of neuronal survival, and the lack of neurogenesis in the hippocampus.[26] Some researchers have demonstrated that vitamin K has antioxidant, anti-inflammatory, anti-apoptotic, and free radical scavenging properties to be the potential neuroprotective therapeutic strategy.[27] Moreover, vitamin K has the therapeutic benefits by improving blood lipid profiles, oxidative stress as well as markers of inflammation.[28] Therefore, it has been considered one of the possible pathogenetic causes of depression.

Additionally, we found that vitamin K is positively and significantly associated with TSH, TC, LDL, and sdLDL levels. Oral vitamin K antagonists (VKAs) have been shown to alter TSH levels in elderly hospitalized patients,[29] a variable directly linked to the development of depression.[30] Moreover, vitamin K might positively impact serum lipids and lipid metabolism.[31] In addition to its anti-inflammatory and antioxidant properties, vitamin K plays a role in nervous system function by regulating sphingolipid metabolism and the distribution of lipids in brain cell membranes.[32] Therefore, vitamin K intake might have a role in reducing the risk of depression and suicidal attempts. The present study has some limitations. First, because our study is case-control, we could not adjust the effects of dietary vitamin K intake due to unavailable nutritional data. Second, our study results should be interpreted cautiously due to the small sample size. Finally, a causal relationship between serum vitamin K levels and suicidal attempts in depressive patients can not be concluded due to the observational nature of the study. Moreover, we explored that in depressive patients with suicidal attempts serum vitamin K was correlated with specific clinical features and the development of suicide. We though that low vitamin K levels in depressed cases would be correlated with less favorable clinical characteristics and subsequent suicidal attempts.

Conclusion

In summary, the current study suggests that serum vitamin K levels in depressive patients with suicidal attempts were significantly lower than in those without suicidal attempts. In addition, low vitamin K levels can characterize suicidal attempts in depressed patients. Moreover, vitamin K levels were closely associated with thyroid dysfunction and the normal metabolism of lipids in depressed patients. Hypovitaminosis K may represent an underlying biological risk factor for the development of depression.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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