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Review Article

The Effect of Vitamin K Supplementation on Glycemic Indices in Adults: A Systematic Review and Meta-Analysis of Clinical Trials

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ABSTRACT

Background: Vitamin K supplementation was shown to be effective on glucose hemostasis and insulin sensitivity in some previous studies, but the results are controversial. The purpose of this meta-analysis was to investigate the effect of vitamin K supplementation on glycemic indices including fasting blood sugar (FBS), hemoglobin A1c (HbA1c), fasting insulin (FI), homeostatic model assessment for insulin resistance (HOMA-IR), quantitative insulin-sensitivity check index (QUICKI) and homeostasis model assessment of β-cell function (HOMA-β).

Methods: The systematic search of literatures was performed on electronic databases of PubMed, Scopus, and Web of Science databases up to December, 2024. The weighted mean difference (WMD) and 95% confidence intervals (95% CI) were calculated to evaluate the pooled effect size using the random-effect model. The heterogeneity was evaluated using I-square (I^2) statistics. Subgroup analysis was done to evaluate the potential sources of heterogeneity.

Results: Among all of the eligible studies, six randomized clinical trials (RCTs) were included in this meta-analysis. The results showed a significant effect of vitamin K supplementation on some glycemic indices including FI (WMD: -1.87; 95% CI: -2.64, -1.09), HbA1c (WMD: -0.89; 95% CI: -1.40, -0.38) and HOMA-IR (WMD: -0.35; 95% CI: -0.39, -0.31). Also, the effect of vitamin K supplementation on other glycemic indices including FBS (WMD: -4.74; 95% CI: -10.56, 1.09), HOMA-β (WMD: -0.36; 95% CI: -1.44, 0.73) were not a significant effect.

Conclusion: The findings of this study indicated that vitamin K supplementation can positively affect FI, HbA1c, and HOMA-IR levels.

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Introduction

The decline in Covid-19's global prevalence has led to resurgence in the importance of non-communicable diseases (NCDs) in human societies. Epidemiological studies have declared that more than 75% of deaths have been caused by NCDs (1) and diabetes mellitus has been considered as the fourth prevalent NCDs (2). By 2045, it has been predicted that 693 million adults will be affected by diabetes (3). While chronic hyperglycemia is accompanied by vascular (microvascular or macrovascular) and non-vascular complications and a higher rate of mortality, there is an urgent need to reduce its rate in the society (3, 4). Several hereditary and modifiable factors including sedentary lifestyle, poor dietary habits, obesity, and smoking may cause diabetes (5, 6). Likewise, dietary factors have a significant impact on the control of glycemic status. However, foods with higher content of carbohydrates, saturated fats, high glycemic index and lower fiber, are associated with a higher risk of hyperglycemia and glucose intolerance (7-12). Also, some micronutrients such as vitamins D, C, and E, as well as zinc, selenium, and magnesium have protective effects against diabetes (13-18).

Furthermore, some studies have investigated the effects of vitamin K on glycemic status (13, 19, 20). Vitamin K as a fat-soluble vitamin has two natural forms: menaquinone (vitamin K_2) and phylloquinone (vitamin K_1) (21). It is mostly known for its role in blood coagulation (22) and prevention of bone fractures (23). It prevents bone fractures by gamma carboxylation of osteocalcin and stimulating the production and secretion of osteocalcin from osteoblasts (24). In addition, some studies have investigated its role on glucose homeostasis and insulin sensitivity (22, 25, 26). The efficacy of vitamin K on various glycemic indices such as fasting blood sugar (FBS), and hemoglobin A1c (HbA1c), as well as insulin sensitivity indices such as homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin (FI), quantitative insulin-sensitivity check index (QUICKI) and homeostasis model assessment of β-cell function (HOMA-β) have been investigated in interventional studies. Nevertheless, their results are contradictory (27-29). Rahimi *et al.* indicated that vitamin K supplementation significantly decreased FBS and HbA1c levels (28). In contrast, the results of two other studies were not consistent with them (27, 30). The underlying mechanism for the effect of vitamin K is that, it may increase carboxylated osteocalcin which cause insulin sensitivity (31). Also, Tarkesh *et al.* showed that vitamin K supplementation may improve HOMA-IR and HOMA-β levels (30). According to contradictory results in term of vitamin K supplementation and glycemic status (27-30), this systematic review and meta-analysis aimed to clarify direction and its effect on FBS, FI, HbA1c, HOMA-IR, HOMA-β and QUICKI levels.

Materials and Methods

This meta-analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (32).

Data Sources and Search Strategy

Relevant studies were searched through electronic databases including PubMed, Scopus, and Web of Science (WOS) from inception up to December, 2024. The following MeSH terms and their associated keywords were searched in the title and abstract: ("vitamin k" OR "vitamin k supplement*" OR phylloquinone OR menaquinone* OR menadione OR "vitamin k1" OR "Vitamin K 1" OR Phyllohydroquinone OR Aquamephyton OR "Vitamin K Quinone" OR "vitamin k2" OR "vitamin K 2" OR "vitamin k3" OR "vitamin K 3" OR Vicasol OR vikasol OR konakion OR phytonadione OR phytomenadion OR mephyton) AND ("Diabetes mellitus" OR "blood glucose" OR "blood sugar" OR "fasting blood sugar" OR "glycemic control" OR "HbA1c" OR "Hb A1c" OR "HOMA-IR" OR "Homeostatic Model Assessment for Insulin Resistance" OR hyperglycemia* OR insulin OR "Glycosylated hemoglobin A" OR "Glycosylated hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "Glycated Hemoglobin A1c" OR "glycohemoglobin A" OR "Glycated Hemoglobins" OR glucose OR "glucose intolerance" OR diabetes OR diabetic* OR "insulin resistance" OR "insulin sensitivity" OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "insulin secretion" OR "B-cell function"). Additionally, the references of related articles were reviewed to identify any missing relevant studies.

Eligibility Criteria and Study Selection

The results of literature review were first imported to EndNote software (version X8, for Windows, Thomson Reuters, Philadelphia, PA, USA). Likewise, duplicates were removed and screening was conducted based on title and abstract. Two authors (SKH and FMS) screened and evaluated the articles independently and discussed any discrepancies. The inclusion criteria were (i) clinical trials; (ii) adult participants (age >18 years); (iii) oral supplementation of vitamin K in any form; (iv)

inclusion of a placebo group; and (v) assessment of at least one of indices including FBS, plasma glucose, FI, HbA1c, HOMA-IR, and HOMA-β. Non-English language studies and studies that co-supplemented vitamin K with other nutrients were excluded from the present review.

Data Extraction

Two independent researchers (SKH and FMS) extracted the characteristics of the first author's name, publication year, country of origin, study design, gender, age, the health status of the subjects, sample size, type and dosage of the intervention, and duration of the intervention. The mean values and standard deviations (SDs) of FBS, FI, HOMA-IR, and HOMA-β were also collected at baseline of the studies and after the intervention. When the variables were measured at several time points during the study, only the baseline and final values were used. The disagreements were resolved through a team meeting.

Quality Assessment

The quality of the studies was evaluated by two researchers (SKH and FMS) using Cochrane risk of bias tool (33). Seven domains of risk of bias tool including selection bias (random allocation and allocation concealment), reporting bias (outcome reporting), performance bias (blinding of personnel and participants), detection bias (blinding of outcome assessment), attrition bias (loss to follow-up) and other biases were assessed. The items were scored as low, high, or unclear risk of bias.

Statistical Analysis

Changes in the mean and 95% confidence intervals (95% CIs) of FBS, FI, HbA1c, HOMA-IR and HOMA-β, in the intervention and control groups, were used to calculate the overall weighted mean difference (WMD) and 95% CI using the random-effects model. Cochran's Q test and I-squared statistics were used to evaluate the between-study heterogeneity (significant heterogeneity was considered when I^2 was greater than 50%). Furthermore, subgroup analysis was conducted to identify possible sources of heterogeneity. Fixed-effect analysis was utilized for all subgroup analyses. A sensitivity analysis was performed to determine if any specific study had a significant effect on the final findings. Publication bias was assessed through visual inspection of funnel plots and confirmed using Egger's regression test. STATA (version 11.0) was employed for all statistical analyses.

Results

The Literature Search and Study Selection

Figure 1 schematically depicts the study selection process. A total of 6216 articles were identified in

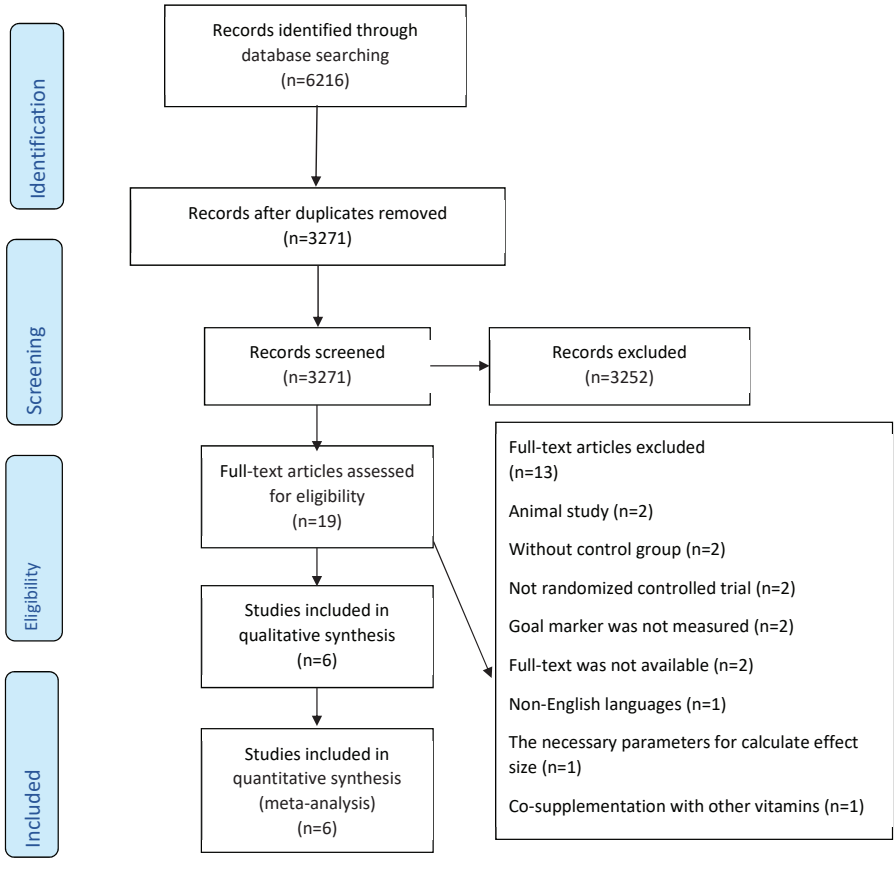

Figure 1: PRISMA flow diagram of study selection process.

the primary search. After eliminating the duplicate papers, 3271 articles remained for title and abstract screening. We excluded 3252 articles due to reasons such as non-interventional design, irrelevant articles, animal studies, and other types of documents (book, letter, etc.). Then, the full-texts of 19 articles were screened. Thirteen studies were excluded for reasons including non-English articles (34); study on rats (35-37); co-supplementation (38); not measuring the specified markers (31, 39); not being RCT (40, 41); absence of control group for comparison (26, 42); lack of available full-texts (43, 44); and the impossibility to determine the effect size (45).

Study Characteristics

Characteristics of all six included studies were presented in Table 1. All six studies were conducted in Iran from 2015 to 2024. The participants' mean age ranged from 27.16 to 63.15 years. The vitamin K dosage ranged from 90 to 1000 mcg/day. The eligible studies included diabetic (n=4) (28, 46-48), pre-diabetic (n=1) (27), and polycystic ovary syndrome (PCOS) patients (n=1) (30).

Systematic Review Results

According to Cochrane guidelines, since less than three studies examined the impact of vitamin K supplementation on QUICKI, we reported it systematically.

Impact of Vitamin K supplementation on QUICKI

Two studies investigated the effect of vitamin K supplementation on QUICKI (28, 30). According to Rahimi Sakak *et al.*, QUICKI level was not significantly altered by vitamin K supplementation (28). However, Tarkesh *et al.* showed an increase in QUICKI level based on vitamin K supplementation when compared to the placebo group (30).

Table 1: Characteristics of six studies conducted in Iran from 2015 to 2024.

First author, year	Country	Study design	Sample size (intervention, control)	Gender (n) (male, female)	Health status	Mean age (years)	Mean BMI (kg/m^2)	Type of administration	Duration of intervention (week)	Dose (mcg/d)
Karamzad, 2020	Iran	Double-blind placebo-controlled randomized clinical trial	Treatment=23, control=22 (45)	Male (31) Female (14)	Diabetic	46.13	30.47	MK-7	12	200
Rahimi Sakak, 2020	Iran	Double-blinded, placebo-controlled, randomized trial	Treatment=32, control=23 (55)	Male (26) Female (42)	Insulin-independent patientswith diabetes	57.7	27.64	MK-7	12	360
Resekhi, 2015	Iran	Randomized, double-blinded, placebo controlled clinical trial	Treatment=39, control=43 (82)	Female (82)	Prediabetes	40.16	28.08	Vitamin K1 (softgel capsule)	4	1000
Tarkesh, 2020	Iran	Randomized, double-blind, placebo-controlled clinical trial	Treatment=42, control=42 (84)	Female (84)	PCOS patients	27.16	26.62	MK-7	8	90
Zhang, 2023	China	Randomized, double-blind, placebo-controlled clinical trial	Treatment=30, control=30 (60)	Male (29) Female (31)	Type 2 diabetes mellitus patients	63.15	25.19	MK-7	24	90 mcg in 100 g yogurt
Amani, 2023	Egypt	Randomized, double-blind, placebo-controlled clinical trial	Treatment=45, control=45 (90)	Male (10) Female (80)	Type 2 diabetes mellitus patients	51.39	35.01	Menadiol diacetate	24	1000

FI: Fasting insulin, FBS: Fasting blood sugar, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin-sensitivity check index, 2H-post-OGTT glucose: 2-h post oral glucose tolerance test, HbA1c: Hemoglobin A1c.

Meta-analysis Results

Impact of Vitamin K supplementation on FBS Level

A pooled analysis of the six effect sizes showed a non-significant reduction in FBS concentration following vitamin K supplementation (WMD: -4.74; 95% CI: -10.56, 1.09) with an average heterogeneity among the studies (I^2=55.1%, p=0.049) (Figure 2). After subgroup analysis, there was no difference in the effects of vitamin K supplementation on FBS level between studies with different types and doses of supplements. Although, the impact of vitamin K on FBS level was significant in studies with longer duration (WMD: -15.25; 95% CI: -28.7, -1.8) and older adults (WMD: -16.33; 95% CI: -27.96, -5.29). The overall meta-analysis results for FBS level was not influenced by specific studies.

Impact of Vitamin K supplementation on Fasting Insulin Level

Following pooling the effect sizes of the six studies, the vitamin K group had a significant decrease in fasting insulin level when compared to the control group (WMD: -1.87; 95% CI: -2.64, -1.09). We conducted subgroup analysis due to significant heterogeneity between the included studies (I^2= 65%, p=0.01) (Figure 3). No differences were observed in the sub-group analysis based on age (participants aged ≥55 years and <55 years) and supplementation duration (more than 12 weeks and 12 weeks or less). A significant reduction in FI level was detected in vitamin K group when compared to placebo group in studies with vitamin k dose ≤500 mcg/day and studies were done by menaquinone (WMD: -2; 95% CI: -2.24, -1.77) (Table 2).

Impact of Vitamin K supplementation on HbA1c Level

Four studies investigated the impact of vitamin K supplementation on HbA1c level (28, 29, 47, 48). We showed a significant decrease in levels of HbA1C (WMD: -0.89; 95% CI: -1.40, -0.38) after supplementation with vitamin K (Figure 4). The sub-group analysis did not reveal any differences among age groups (participants aged ≥55 years and <55 years) and supplementation duration (more than 12 weeks and 12 weeks or less) (Table 2). Studies were done by menaquinone (WMD; -0.77; 95% CI: -0.90, -0.63) and dose ≤500 mcg/day (WMD; -0.77; 95% CI: -0.90, -0.63) showed a significant reduction in HbA1c level, but this effect was not observed for menadiol diacetate (WMD; -0.17; 95% CI: -0.73, 0.39).

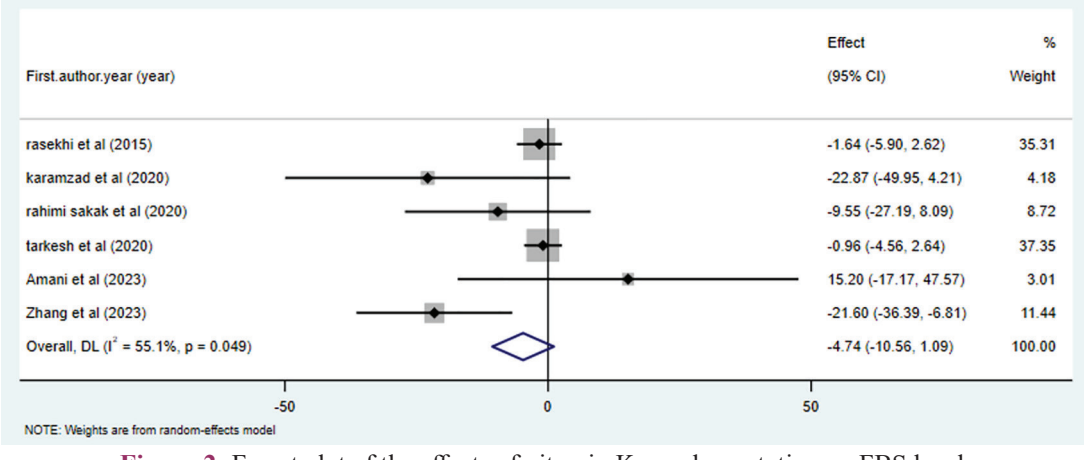

Figure 2: Forest plot of the effects of vitamin K supplementation on FBS level.

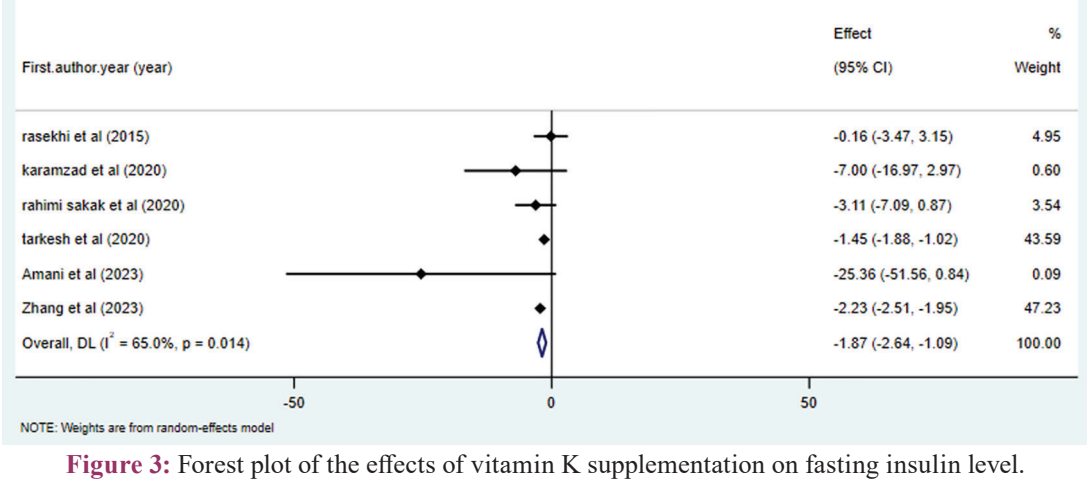

Figure 3: Forest plot of the effects of vitamin K supplementation on fasting insulin level.

Table 2: Subgroup analyses to assess the effect of vitamin K supplementation on glycemic markers.

Variable	Sub-grouped by	No. of trials	Effect size	95% CI	I^2 (%)	*P* value for heterogeneity	*P* value for between subgroup heterogeneity[2]
FBS	Mean age						0.01
	≤55 years	4	-1.35	-4.07, 1.38	14.1	0.32	
	>55 years	2	-16.63	-27.96, -5.29	5	0.3	
	Intervention dose						0.62
	≤500 mcg/day	4	-2.72	-6.12, 0.68	69.6	0.02	
	>500 mcg/day	2	-1.35	-5.58, 2.88	2.1	0.31	
	Duration of studies						0.05
	≤ 12 weeks	4	-1.65	-4.36, 1.05	8.3	0.35	
	<12 weeks	2	-15.25	-28.7, -1.8	75.7	0.04	
	Supplementation type						0.53
	Menaquinone	4	-2.72	-6.12, 0.68	69.6	0.02	
	Phyloquinone	1	-1.64	-5.9, 2.62	0	Less than 0.001	
	Menadiol diacetate	1	15.2	-17.17, 47.57	0	Less than 0.001	
HbA1c	Mean age						0.003
	≤55 years	2	-0.75	-1.11, -0.38	86.2	0.007	
	>55 years	2	-0.73	-0.87, -0.59	84.3	0.012	
	Intervention dose						0.003
	≤500 mcg/day	3	-0.77	-0.090, -0.63	78.8	0.009	
	>500 mcg/day	1	-0.17	-0.73, 0.39	0	0.001	
	Duration of studies						0.003
	≤ 12 weeks	2	-1.35	-1.80, -0.90	59.8	0.115	
	12 weeks <	2	-0.68	-0.81, -0.54	70.5	0.066	
	Supplementation type						0.003
	Menaquinone	3	-0.77	-0.90, -0.63	78.8	0.009	
	Menadiol diacetate	1	-0.17	-0.73, 0.39	0	<0.001	
FI	Mean age						0.003
	≤55 years	4	-1.45	-1.87, -1.02	30.7	0.17	
	>55 years	2	-2.23	-2.52, -1.95	0	0.66	
	Intervention dose						0.89
	≤500 mcg/day	4	-0.35	-0.39, -0.31	57.9	0.07	
	>500 mcg/day	2	-0.48	-2.37, 1.4	64.4	0.09	
	Duration of studies						0.003
	≤ 12 weeks	4	-1.46	-1.88, -1.03	0	0.48	
	12 weeks <	2	-2.23	-2.52, -1.95	66.6	0.08	
	Supplementation type						0.12
	Menaquinone	4	-2	-2.24, -1.77	70.1	0.01	
	Phyloquinone	1	-0.16	-3.47, 3.15	0	0.001	
	Menadiol diacetate	1	-25.36	-51.56, 0.84	0	0.001	
HOMA-IR	Mean age						0.024
	≤55 years	4	-0.14	-0.33, 0.05	17.1	0.3	
	>55 years	2	-0.36	-0.4, -0.32	17.2	0.27	
	Intervention dose						0.89
	≤500 mcg/day	4	-0.35	-0.39, -0.31	57.9	0.06	
	>500 mcg/day	2	-0.48	-2.37, 1.4	64.4	0.09	
	Duration of studies						0.03
	≤12 weeks	4	-0.15	-0.34, 0.04	0	0.46	
	12 weeks <	2	-0.36	-0.4, -0.32	64.1	0.095	
	Supplementation type						0.24
	Menaquinone	4	-0.35	-0.39, -0.31	57.9	0.06	
	Phyloquinone	1	-0.17	-2.09, 1.75	0	Less than 0.001	
	Menadiol diacetate	1	-8.79	-18.69, 1.11	0	Less than 0.001	

Variable	Sub-grouped by	No. of trials	Effect size	95% CI	I^2 (%)	*P* value for heterogeneity	*P* value for between subgroup heterogeneity[2]
HOMA-β	Mean age						0.88
	≤55 years	2	-0.39	-1.53, 0.76	0	0.58	
	>55 years	2	-0.12	-3.34, 3.1	0	0.38	
	Intervention dose						0.58
	≤500 mcg/day	3	-0.36	-1.44, 0.72	0	0.67	
	>500 mcg/day	1	20.39	-54.13, 94.91	0	Less than 0.001	
	Duration of studies						0.76
	≤ 12 weeks	3	-0.41	-1.56, 0.74	0	0.6	
	12 weeks <	1	0.11	-3.15, 3.37	0	Less than 0.001	
	Supplementation type						0.58
	Menaquinone	3	-0.36	-1.44, 0.72	0	0.67	
	Phyloquinone	1	20.39	-54.13, 94.91	0	Less than 0.001	

FBS: Fasting blood sugar; FI: Fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance; HOMA-β, homeostatic model assessment for β-cell function, 95% CI: 95 % confidence interval.

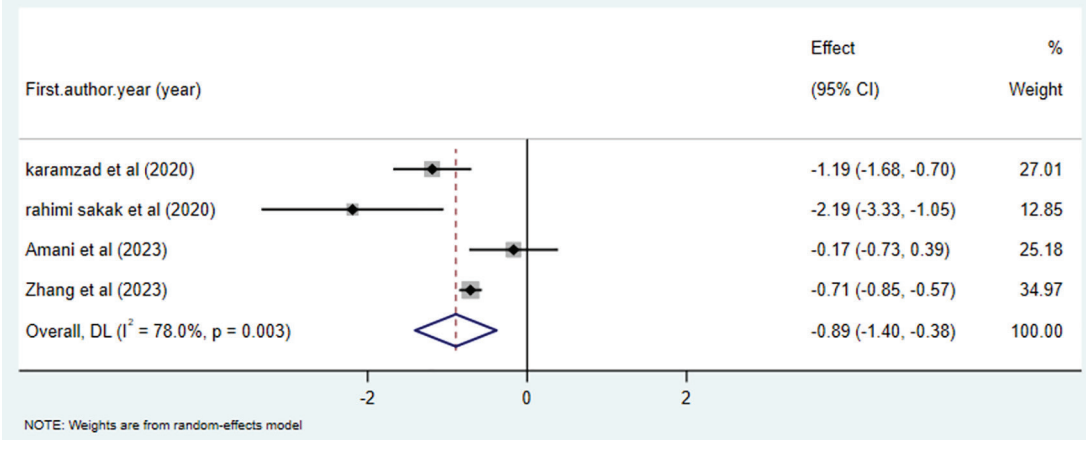

Figure 4: Forest plot of the effects of vitamin K supplementation on HbA1C level.

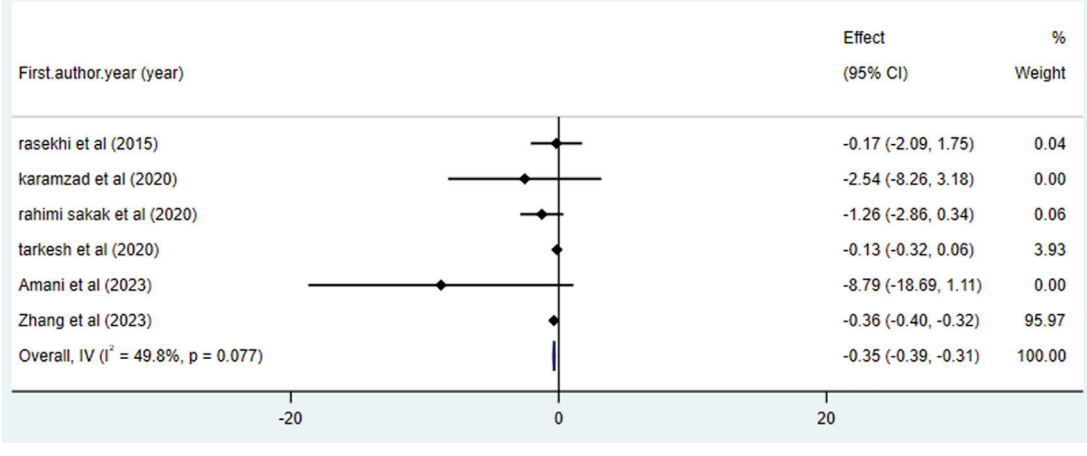

Figure 5: Forest plot of the effects of vitamin K supplementation on HOMA-IR level.

Impact of Vitamin K supplementation on HOMA-IR Level

After combining the results of the six studies, we detected a significant reduction in HOMA-IR level (WMD: -0.35; 95% CI: -0.39, -0.31) following vitamin K supplementation (Figure 5). The effect of vitamin K on HOMA-IR level was significant in studies with longer duration (more than 12 weeks) and older participants (participants aged ≥55 years) (Table 2). Also, studies were done by menaquinone and with lower dosage (less than 500 mc per day) showed a significant reduction in HOMA-IR level.

Impact of Vitamin K supplementation on HOMA-β Level

The pooled analysis of four effect sizes revealed no significant change in HOMA-β level after vitamin K supplementation (WMD: -0.36; 95% CI: -1.44, 0.73).

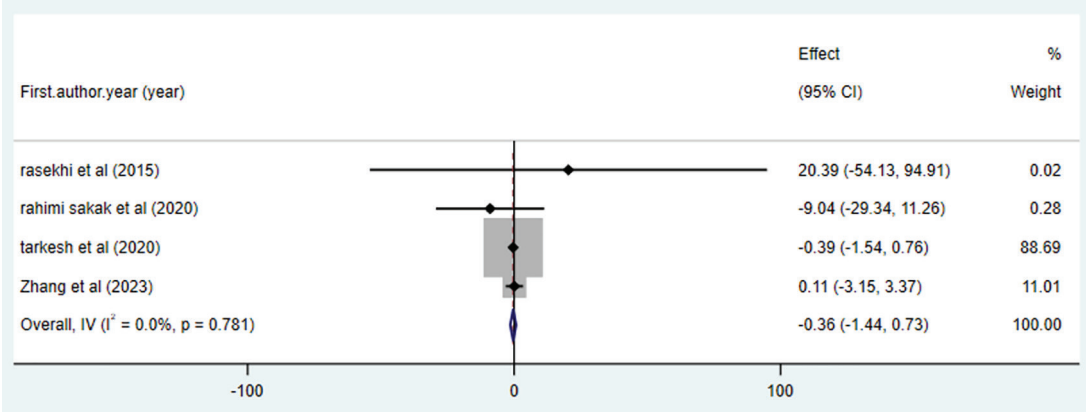

Figure 6: Forest plot of the effects of vitamin K supplementation on HOMA-β level.

Table 3: Quality assessment using Cochrane risk of bias tool.

Authors	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Conflict of interest	Chance bias (baseline imbalance)
Karamzad *et al.*	L	L	L	U	L	L	L	L	L
Rahimi sakak *et al.*	L	U	L	L	L	L	H	L	L
Rasekhi *et al.*	U	U	H	U	L	L	U	L	L
Tarkesh *et al.*	L	U	L	U	L	L	L	L	L
Zhang *et al.*	U	U	L	L	L	L	U	L	L
Amani *et al.*	L	L	L	L	L	L	L	L	L

L: Low risk of bias; H: High risk of bias; U: Unclear risk of bias

A low heterogeneity was seen between the included studies (I^2=0.00%, p=0.781) (Figure 6). No significant distinction existed between studies with a mean age ≤55 years and >55 years. Moreover, there was no significant difference between the studies with vitamin k dose ≤500 and >500 mcg/day.

Quality Assessment

Table 3 contains the results of the Cochrane quality assessment. Two domains of quality assessment tool including blinding of participants and personnel and blinding of outcome assessment obtained lower risk of bias in all included studies. Rasekhi *et al.* and Rahimi *et al.* got higher risk of bias for selective reporting and incomplete outcome data, respectively (28, 49).

Discussion

According to recently published RCTs that have evaluated the impact of vitamin K supplementation on glycemic indicators with contradictory results, we decided to conduct an up-to-date systematic review and meta-analysis to clarify the direction of vitamin K treatment on glycemic status (14, 50-52). In this meta-analysis, vitamin K supplementation significantly improved FI, HbA1c and HOMA-IR levels; but no statistically significant effect was observed in FBS, and HOMA-β levels. In this regard, several mechanisms have been considered for the possible effect of vitamin K supplementation on glycemic control. Evidence indicated that vitamin K treatment may decrease the level of inflammatory cytokines including leptin, interlukine-6 (IL-6), and tumor necrosis factor-α (TNF-α), which are involved in insulin resistance, subsequently (53-55).

It was shown that elevated leptin is linked to obesity-related complications, which could lead to insulin resistance (56). Similarly, IL-6 is correlated with hyperglycemia and it can suppress the transcription of adiponectin (57). On the other hand, it was pointed to anti-inflammatory and anti-diabetic effects of adiponectin that may be affected by vitamin K levels (55). In addition, the role of

vitamin k in the control of glycemic status is possible through decreased cholesterol and low-density lipoprotein cholesterol (LDL-C) and increased high-density lipoprotein cholesterol (HDL-C). It has been demonstrated that decreased cholesterol and (LDL-C) and increased (HDL-C) may contribute to the regulation of plasma glucose and insulin levels (58-60). Furthermore, osteocalcin as vitamin K-dependent bone protein has been associated with decreased risk of diabetes. A previous study showed that osteocalcin (ucarboxylated form) may improve insulin secretion (49). Accordingly, the risk of chronic diseases, such as type-2 diabetes mellitus (T2DM), may be reduced by the beneficial properties of vitamin K. Beulens *et al.* illustrated that individuals with higher intake of vitamin K had 19% lower risk of diabetes (61).

In other studies, vitamin K supplementation in PCOS patients significantly reduced HOMA-IR level (30, 62). However, Rasekhi *et al.* (27) and Shahdadian *et al.* (14) did not observe such effects. The reason for this discrepancy can be explained by different period of supplementation or type of vitamin K (vitamin K1 or K2) used in the two studies by them (14, 27). Moreover, this discrepancy may be due to the different health status of the participants. In Tarkesh *et al.*'s study (30), the participants were suffering from PCOS vs. prediabetic patients in Rasekhi *et al.*'s study (27). As a result, the difference in the initial values of insulin resistance in the participants may have caused distinct results.

In addition, the present systematic review determined no significant impact of vitamin K treatment on HOMA-IR and HOMA-β levels. These results may be attributed to several issues. However, vitamin K is stored in adipose tissue and the mean BMI of participants in all included studies are over 25 kg/cm^2. Likewise, the bioavailability of vitamin K to exert its beneficial effects can be affected by larger adipose tissue of participants (63); as most of included studies are elderlies that may have lower number of osteoblasts to form osteocalcin (55). Also, the phenomenon of insulin resistance is age-dependent that may be promoted by elderly participants of our study.

The studies of Karamzad *et al.* (29) and Rahimi *et al.* (28) showed that supplementing with vitamin K2 caused a significant decrease in fasting glucose. However, Choi *et al.* (31) failed to find a significant improvement on FBS level in 42 healthy young men following 4 weeks of vitamin K2 treatment at a dose of 30 mg. In other studies that were conducted among only women, vitamin K had no significant effect on FBS level (49, 62). Similarly, Choi *et al.* performed such study among men which was accompanied with a non-significant effect on FBS level (31). In contrast, two other studies that were completed among both men and women, resulted in a significant decline in FBS level (28, 29). Besides, Yoshida *et al.*'s observational study (40), which had included more participants than Rahimi *et al.* (28) and Karamzad's *et al.*'s (29) studies and included both sexes, the effect of vitamin K intake on FBS level was seen only in men. Therefore, one of the reasons for observing these inconsistencies may be the larger sample size and gender differences of the participants. Also, the mean age of the participants in Yoshida *et al.*'s study (40) was much higher than other studies.

As, Yoshida *et al.* (40) evaluated the effects of vitamin K1 intake on insulin sensitivity and glycemic status in a larger population of men (n=1247) and women (n=1472) for 12 months. In this study, 2-hr post oral glucose tolerance test (OGTT) insulin, 2-hr post OGTT glucose and the insulin sensitivity index improved in subjects who consumed more vitamin K1. However, vitamin K1 intake did not significantly affect FBS, FI, HbA1c, and HOMA-IR levels. Although intake vitamin K could affect 2-hr post OGTT insulin and glucose levels, there was still no obvious explanation for why it could not significantly alter such values during the fasting period. However, it may be due to the delay in the increase of glucose and insulin concentration in response to glucose intake in subjects who have lower intake of vitamin K1.

In the same line with our study, the results of a review by Shahdadian *et al.* (14), did not support the effect of vitamin k supplementation on HOMA-β level. Rasekhi *et al.* (27) concluded that vitamin K supplementation did not significantly affect FBS, HOMA-β, or FI levels in 82 pre-diabetic women after 4 weeks of supplementation. However, Tarkesh *et al.* (30) showed that HOMA-β, and FI levels significantly decreased and QUICKI significantly increased in 84 patients with PCOS following 8 weeks of vitamin K supplementation. This means that supplementation with vitamin K has reduced insulin secretion as well as insulin resistance in the patients.

The strengths of the present meta-analysis were subgroup analysis based on the dose of vitamin K, the duration of the intervention and the mean age of the participants, and investigating several glycemic parameters. On the other hand, some of the limitations of this study were the small number of studies that were included, the amount of dietary vitamin K that was not taken into account in most of studies, the baseline serum level of vitamin K that was not measured, and the body mass index (BMI) and body fat percentage of the participants which were not taken into account in the studies as

these variables affected the availability of vitamin K. Also the vast majority of studies were originated from Iran; thus, extrapolation of these results to other populations can be questionable.

Conclusion

In the present meta-analysis, vitamin k supplementation showed a significant beneficial effect on HOMA-IR, HbA1c and FI levels. However, no significant effects were observed in term of FBS and HOMA-β levels. Better and more conclusive judgments require performing larger and well-designed RCTs.

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Authors' Contribution

S.KH, M.M and N.H designed the research; S.KH and F.M.S. were responsible for conducting the electronic search; S.KH, F.M.S independently identified the eligible study and extracted information; the data was analyzed and interpreted by A.E and M.M and M. Moazen; all authors contribute to write the manuscript draft, the manuscript revise and approve the final version of the manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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