

Effect of vitamin K supplementation on insulin sensitivity: a meta-analysis

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Objective: To perform a systematic review and meta-analysis of randomized, placebo-controlled trials to assess the effect of vitamin K supplementation on insulin sensitivity.

Data sources: MEDLINE, the Cochrane Library, CINAHL, Web of Science, Scopus, clinicaltrials.gov, and clinicaltrialsresults.org were searched up to January 2017. Reference lists of related papers were also scanned.

Study selection: Randomized controlled trials were selected if they compared vitamin K supplementation with placebo or no treatment and reported homeostasis model assessment of insulin resistance, fasting plasma glucose, fasting plasma insulin, C-reactive protein, adiponectin, leptin, or interleukin-6 levels.

Data extraction: Data extraction and study quality assessment were performed independently by two investigators using a standardized data extraction form. Any inconsistencies were resolved by a third reviewer. Effect estimates were pooled using inverse-variance weighted method. Heterogeneity was assessed by the I^2 and Q statistic.

Results: A total of eight trials involving 1,077 participants met the inclusion criteria. A wide variety of participants were enrolled, including older men, postmenopausal women, prediabetic premenopausal women, and participants with a history of diabetes, hypertension, or vascular disease. Vitamin K1 and vitamin K2 (MK-4 and MK-7 subtypes) were assessed. Supplementation period ranged from 4 weeks to 3 years. Vitamin K supplementation did not affect insulin sensitivity as measured by homeostasis model assessment of insulin resistance, fasting plasma glucose, fasting plasma insulin, C-reactive protein, adiponectin, leptin, and interleukin-6 levels.

Conclusion: Our analysis suggests no effect of vitamin K supplementation on insulin sensitivity.

Keywords: vitamin K, insulin resistance, meta-analysis, systematic review

Introduction

Bone has been well established as an endocrine organ.^{1,2} Its noncollagenous skeleton hormone named osteocalcin has been positively associated with physical activity³ and insulin sensitivity.^{4,5} Reduced serum concentration of osteocalcin has been linked to an increased risk of diabetes,^{6,7} which, in turn, has been linked to an increased risk of fracture.⁸⁻¹⁰ Vitamin K represents a group of naphthoquinone derivatives (isoprenoid quinones) that are well known for their role in hemostasis. Various forms of vitamin K can be obtained mainly from diet. Leafy greens contain high amount of vitamin K1 (phylloquinone). Dairy products, cheese, and fermented food contain vitamin K2 (menaquinone). Notably, the Japanese food “natto” is extremely rich in vitamin K2 (MK-7 subtype). All forms of vitamin K act as a cofactor for posttranslational modification of proteins.^{11,12} Apart from cofactor function,

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vitamin K also plays putative roles in osteoporosis, vascular calcification, cancer, glucose metabolism, and insulin resistance.¹³ Several studies have reported the beneficial effects of vitamin K on insulin sensitivity, metabolic syndrome, glucose homeostasis, and in reducing the risk of diabetes.^{14–20} Moreover, vitamin K has been demonstrated to decrease cytokines and inflammatory markers, which are implicated in the pathology of insulin sensitivity.^{21–24} The underlying mechanisms of vitamin K on insulin sensitivity have not yet been well established. It has been postulated that vitamin K-dependent bone protein osteocalcin, also known as bone γ -carboxyglutamic acid protein, functions as a mediator in the endocrine pathway. This could influence insulin sensitivity by acting directly on pancreatic β cells, increasing their proliferation and insulin secretion. Bone γ -carboxyglutamic acid protein can increase energy expenditure and adiponectin secretion from adipocytes.^{25–28} Clinical trials of vitamin K supplementation have reported conflicting results on its effect on insulin sensitivity.^{20,29,30–37} We therefore perform a systematic review and meta-analysis of randomized controlled trials to evaluate the effect of vitamin K supplementation on insulin sensitivity.

Methods

This review was conducted and presented as recommended by PRISMA statement.

Data sources

Clinical studies of vitamin K were identified through electronic databases including MEDLINE, The Cochrane Library, CINAHL, Web of Science, Scopus, <http://clinicaltrials.gov>, and <http://clinicaltrialresults.org>. The databases were searched from inception to the end of January 2017 without language restriction. A historical search of reference lists of relevant papers was also conducted. The following MeSH terms were used: vitamin K, phylloquinone, menaquinone, naphthoquinone, insulin resistance, and randomized controlled trials. This was followed by the search terms: [vitamin K or naphthoquinone or phylloquinone or menaquinone] AND [insulin resistance or HOMA-IR or fasting plasma glucose or fasting plasma insulin or C-reactive protein or adiponectin or leptin or interleukin-6].

Study selection

To be included in the systematic review, a study had to be a randomized controlled trial comparing vitamin K supplementation against placebo or no treatment, reporting homeostasis model assessment of insulin resistance (HOMA-IR),

fasting plasma glucose (FPG), fasting plasma insulin (FPI), C-reactive protein (CRP), adiponectin, leptin, or interleukin-6 (IL-6) levels as outcomes.

Data extraction and quality assessment

Data were extracted from individual studies independently by two reviewers using a standardized form. Any discrepancies were resolved by a third reviewer. The data extracted were publication year, country of origin, study characteristics, duration of intervention, dosage and form of vitamin K, sample size, and outcome measures, ie, HOMA-IR, FPG, FPI, adiponectin, leptin, IL-6, or CRP levels. The methodological quality was assessed using the scale developed by Jadad et al.³⁸ The studies with a score of at least three out of five points were considered high quality.

Statistical analysis

The outcome measures were HOMA-IR, FPI, FPG, adiponectin, leptin, IL-6, and CRP levels. Treatment effect was estimated with a mean difference in the change from baseline value (HOMA-IR, FPI, and FPG) or in the final value (adiponectin, leptin, IL-6, and CRP) between the treatment and the control groups, depending on extractable data. Statistical heterogeneity was assessed using the Q statistic and I^2 statistic. Data was combined using the fixed-effects model if heterogeneity was nonsignificant and the random-effects model was used if Q statistic for heterogeneity was significant at the level of 0.1. The inverse variance-weighted method was used for the pooling of mean difference and the estimation of a 95% confidence interval (CI).³⁹ Review Manager Software (RevMan 5.3.5, Cochrane Community, London, UK) provided by the Cochrane Collaboration (Oxford, UK) was used for analyzing data. The significant level was set at $P < 0.05$. Funnel plot to assess publication bias was not performed due to a small number of studies included in the meta-analysis.

Results

Search results and study characteristics

We identified 326 reports through database searching, and 20 papers were retrieved for detailed evaluation. Ten reports were excluded as they were not randomized controlled trials. One randomized controlled trial was further excluded as vitamin K, D, and calcium cosupplementation was compared against placebo.⁴⁰ The remaining nine randomized, placebo-controlled trials^{29,30–37} met the inclusion criteria. However, two papers^{29,32} were duplicate reports. The paper reporting more complete data³² was included, leaving eight

randomized controlled trials in the systematic review and meta-analysis^{30–37} (Figure 1). Of the eight trials, two^{30,35} enrolled the same group of participants, but reported different outcomes. Data from these two studies were separately analyzed. Studies were conducted in England, the USA, Iran, Japan, the Netherlands, and Denmark. The number of participants ranged from 42 to 452. The study duration varied from 4 weeks to 3 years. Vitamin K was compared with placebo or no treatment, although in some studies participants in both the treatment and the control groups were similarly treated with vitamin D³⁶; vitamin D and calcium³¹; or vitamin D, calcium, and multivitamin.^{30,35} Five studies^{30–32,35,36} evaluated vitamin K1 ranging from 500 to 1,000 µg/d. Two trials^{33,34} used vitamin K2 (MK-4) 1.5 and 45 mg/d, and one trial³⁷ assessed vitamin K2 (MK-7) 100 µg/d. Subjects were older men or postmenopausal women who did not have diabetes at baseline.^{30,31,33–36} One trial each enrolled premenopausal women with prediabetes³² and participants with history of diabetes, hypertension, or vascular disease.³⁷ The characteristics of all the trials are tabulated in Table 1. All the studies were regarded as high quality. Table 2 summarizes the outcomes reported by individual studies.

Meta-analysis of effects on HOMA-IR, FPG, and FPI

Three studies^{30–32} with a total of 479 subjects (244 in the vitamin K and 235 in the control groups) reported results on HOMA-IR, FPG, and FPI. Vitamin K supplementation had no effect on HOMA-IR, FPG, and FPI. The pooled mean differences were -0.14 (95% CI: -0.35 to 0.07 , $P=0.19$), 0.30 mg/dL (0.02 mmol/L; 95% CI: -3.11 to 3.70 , $P=0.86$), and -0.34 µIU/mL (95% CI: -1.13 to 0.45 , $P=0.40$) for HOMA-IR, FPG, and FPI, respectively (Figure 2).

Meta-analysis of effect on leptin

Two studies^{32,33} contributed data on the effect of vitamin K supplementation on leptin. Again, leptin did not change with vitamin K supplementation (mean difference = 0.77 ng/mL; 95% CI: -1.32 to 2.86 ; Figure 2).

Meta-analysis of effects on IL-6 and CRP

Vitamin K supplementation failed to show a significant effect on IL-6 or CRP levels. The pooled mean differences were 0.14 pg/mL (95% CI: -0.69 to 0.97) and -0.49 mg/L (95% CI: -1.18 to 0.20) for IL-6 and CRP, respectively (Figure 2).

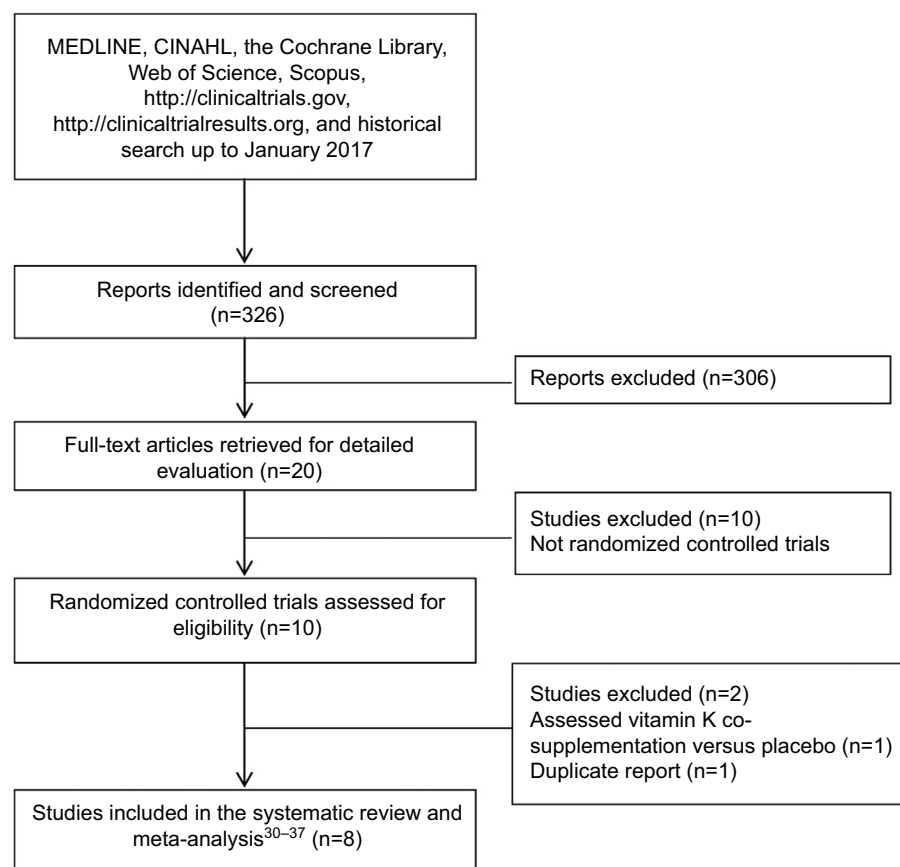


Figure 1 Flow of study selection.

Table 1 Characteristics of the studies included in the systematic review

Study	Country of origin	Study design	Duration	Number of participants (VK:C)	Inclusion criteria	Treatment group	Control group	Quality score	Dietary intake and LSM
Yoshida et al. ³⁰ Shea et al. ³⁵	USA	DB, P	3 years	452 (229:223)	Men and postmenopausal women aged 60–80 years who did not have diabetes at baseline	K1 500 µg/d + multivitamin + calcium carbonate 600 mg/d + vitamin D 400 IU/d	Multivitamin + calcium carbonate 600 mg/d + vitamin D 400 IU/d	4	Subjects were advised to maintain their usual diet and avoid taking dietary supplements other than those provided throughout the study. Mean rate of adherence with treatment, assessed on the basis of pill counts over 3 years, was 89.1% for the treatment group and 88.5% for the control group.
Kumar et al. ³¹	USA	DB, P	1 years	42 (21:21)	Ambulatory, community-dwelling postmenopausal women (>5 years postmenopausal) with a lumbar spine and proximal femur T-score above –2.0 or above –1.5 if a NOF-defined risk factor is present. Had a self-reported low dietary vitamin K intake	K1 1 mg/d + calcium 315 mg (bd) + D3 200 IU (bd)	PLB + calcium 315 mg (bd) + D3 200 IU (bd)	3	NR
Rasekhi et al. ³²	Iran	DB, P	4 weeks	82 (39:43)	Premenopausal women with prediabetes defined as IFG (100 mg/dL < FPG <126 mg/dL) or IGT (140 mg/dL < glucose 120 min <200 mg/dL). Aged 22–45 years, BMI 18.5–30 kg/m ²	K1 1,000 µg/d	PLB	4	Participants were asked to maintain their habitual food consumption, body weight, and physical activity. Subjects were not allowed to consume any supplements other than the one provided by investigator.
Kotaya et al. ³³	Japan	DB, P	1 year	48 (24:24)	Postmenopausal Japanese women aged 50–65 years	K2 (MK-4) 1.5 mg/d	PLB	4	Natto (MK-7 containing fermented soybean) intake was restricted to once or twice a week during study period.
Knapen et al. ³⁴	the Netherlands	DB, P	3 years	325 (161:164)	Healthy, nonosteoporotic postmenopausal Caucasians women aged 55–75 years	K2 (MK-4) 45 mg/d	PLB	4	NR
Kristensen et al. ³⁶	Denmark	DB, CO	6 weeks	48	Postmenopausal women (>5 years since last menses)	K1 500 µg/d + D3 10 µg/d	PLB + D3 10 µg/d	4	Subjects were allowed to consume their habitual diet.
Fulton et al. ³⁷	the Netherlands	DB, P	6 months	80 (40:40)	Community-dwelling people aged ≥70 years with a history of hypertension, diabetes, or previously diagnosed vascular disease.	K2 (MK-7) 100 mcg/d	PLB	4	NR

Abbreviations: bd, twice daily; BMI, body mass index; C, control; CO, crossover; CRP, C-reactive protein; DB, double-blind; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose test; IL-6, interleukin-6; LSM, lifestyle modification; MK-4, menaquinone-4; NOF, National Osteoporosis Foundation; P, parallel; VK, vitamin K; PLB, placebo; NR, not reported; MK-7, menaquinone-7.

Table 2 Summary of outcomes reported in the studies included in the meta-analysis

Author	List of outcomes reported						
	HOMA-IR	FPG	FPI	Adiponectin	Leptin	IL-6	CRP
Yoshida et al ³⁰	√	√	√				
Kumar et al ³¹	√	√	√				
Rasekhi et al ³²	√	√	√	√	√		
Koitaya et al ³³				√	√		
Knapen et al ³⁴				√			
Shea et al ³⁵						√	√
Kristensen et al ³⁶						√	√
Fulton et al ³⁷							√

Abbreviations: CRP, C-reactive protein; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6.

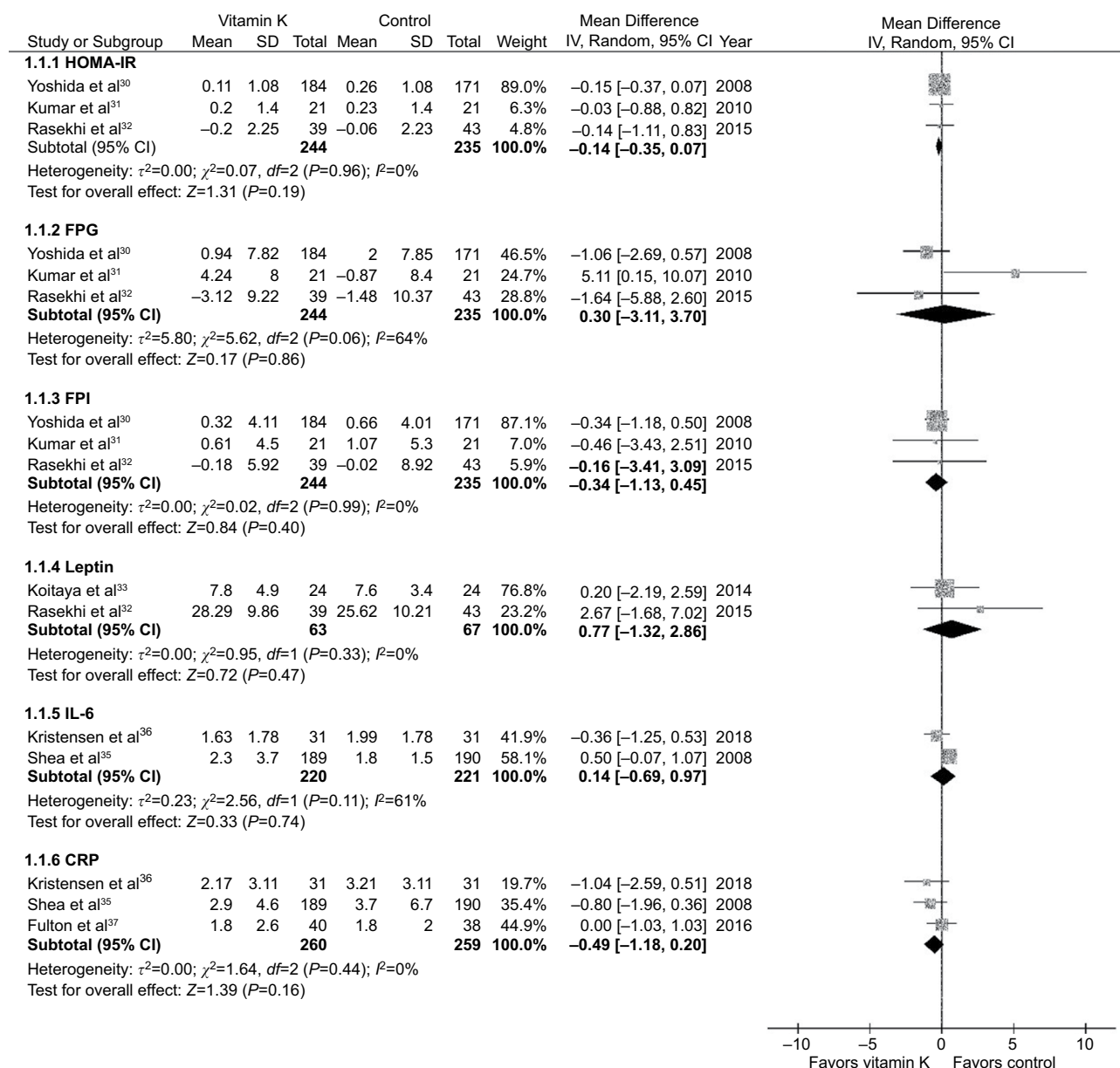


Figure 2 Mean difference (95% CI) in HOMA-IR, FPG, FPI, leptin, IL-6, and CRP.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model of insulin resistance; IL-6, interleukin-6.

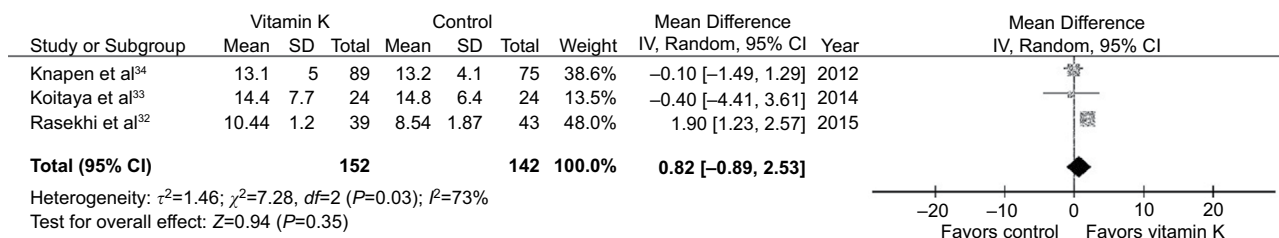


Figure 3 Mean difference (95% CI) in adiponectin.

Abbreviation: CI, confidence interval.

Meta-analysis of effect on adiponectin

Three studies^{32–34} involving a total of 294 subjects (152 in the vitamin K and 142 in the control groups) provided poolable data on adiponectin. No effect of vitamin K supplementation was observed. The pooled mean difference was 0.82 µg/mL (95% CI: -0.89 to 2.53; Figure 3).

Discussion

Several studies have reported vitamin K supplements and its effect on insulin sensitivity. The proposed mechanism is through bone pathway. In in vitro studies, osteocalcin, which is a vitamin K-dependent bone protein, in its uncarboxylated form can increase β cell mass and insulin concentration and promote the release of adiponectin by acting directly on adipocytes,^{2,25} resulting in an increase in sensitivity to insulin. In humans, both carboxylated and uncarboxylated forms of osteocalcin can be presented in circulation. This is the first meta-analysis of the effect of vitamin K supplementation on insulin sensitivity. We focused on both vitamin K1 and vitamin K2 and reported on HOMA-IR, FPG, FPI, adiponectin, leptin, IL-6, and CRP. HOMA-IR developed by Matthews et al⁴¹ is an easy and efficient method used in clinical practice. It can be easily calculated from FPG and FPI. The results of the meta-analysis showed that vitamin K supplementation has no effect on HOMA-IR, FPG, or FPI levels. Heterogeneity was detected in the meta-analysis of FPG ($I^2=64\%$, $P=0.06$). This became nonsignificant when the study by Kumar et al³¹ was excluded ($I^2=0\%$, $P=0.80$). This study enrolled patients with low level of FPG at baseline (mean ± SD: 78.64±9.4 mg/dL), whereas the others^{30–32} included participants with baseline FPG of 93.55–107.66 mg/dL. Variability in treatment interventions may also introduce heterogeneity. Two studies used vitamin K1 500 µg/d³⁰ and 1 mg/d³¹ in addition to calcium and vitamin D for the treatment group and placebo plus calcium and vitamin D for the control group. The other³² used vitamin K1 1,000 µg/d.

Adiponectin is an adipocyte-secreted hormone and has a role as an insulin sensitizer.^{42–44} Again, vitamin K

supplementation did not affect adiponectin level. However, significant heterogeneity existed ($I^2=73\%$, $P=0.03$). This may be due to differences in the characteristics of participants and in the forms and dosages of vitamin K used. Heterogeneity became nonsignificant when the study by Rasekhi et al³² was excluded ($I^2=0\%$, $P=0.89$). In this study, adiponectin level was significantly increased with vitamin K supplementation.³² The observed effect may be attributable to osteocalcin, which acts directly on adipocytes, resulting in adiponectin secretion.^{25–28} This study enrolled participants aged between 22 and 45 years and used vitamin K1 1,000 µg/d,³² while two other studies included participants aged 50–65 and 55–75 years and used vitamin K2 (MK-4) 1.5 and 45 mg/d, respectively.^{33,34} It was reported that elderly women have higher uncarboxylated osteocalcin concentration than younger women,^{45,46} and the amount of vitamin K required for carboxylation of proteins with glutamic acid domains may be higher in older subjects.⁴⁷ This may be due to either an age-related decrease in the number of osteoblasts or the enzymatic activity of γ-carboxylase in osteoblasts.⁴⁷ Vitamin K2 (MK-4) is known to be more lipophilic and is transported to extrahepatic tissues faster than vitamin K1. Vitamin K1 can be converted to vitamin K2 (MK-4) at any rate in extrahepatic tissues, such as pancreas, arterial walls, and testis, by replacing the phytyl side chain with isoprene residues.¹² Long-chain menaquinone, MK-7, has a higher efficacy in carboxylation process and a higher bioavailability compared to MK-4⁴⁸ and is simply more potent than vitamin K1. MK-7-rich food (natto) intake was restricted to once or twice a week in one of our included studies³³ as it may add to the effect of vitamin K supplementation. Clinical trials of MK-7 and insulin sensitivity are currently lacking.

Leptin plays an important role in inflammation, insulin secretion, and insulin sensitivity.⁴⁹ Elevated leptin concentrations are implicated in the etiology of obesity-associated insulin resistance.⁵⁰ CRP is a marker of systemic inflammation. Its causative role in the development of insulin resistance has been suggested.^{51,52} IL-6 is a proinflammatory mediator that

suppresses adiponectin transcription and can induce insulin resistance.^{53,54} Again, meta-analysis results demonstrated no effect of vitamin K on leptin, IL-6, and CRP. Heterogeneity was also detected when analyzing IL-6 data ($I^2=61%$, $P=0.11$). This may be due to variations in study design and intervention between these two studies (Table 1). The available data on leptin and IL-6 are scarce.

It is worth noting that some of the studies included in our meta-analysis were not specifically designed to evaluate the effect of vitamin K on insulin sensitivity. For example, one investigated whether vitamin K2 (MK-4) supplement improved bone metabolism.³³ The other assessed the effect of phylloquinone on blood lipids and inflammatory and fibrinolytic markers.³⁶ In addition, seven^{30,31,33–37} out of the eight included trials enrolled postmenopausal women or elderly men. As insulin sensitivity is known to decrease with age,⁵⁰ this may partly explain an absence of effect of vitamin K supplement observed in our meta-analysis.

Dietary reference intake of vitamin K ranges between 1 and 1.5 $\mu\text{g}/\text{kg}$ body weight/d.¹² Adequate intake of vitamin K1 has been estimated to be 120 $\mu\text{g}/\text{d}$ for men and 90 $\mu\text{g}/\text{d}$ for women.⁵⁵ These recommended ranges are set according to the needs of liver for normal blood coagulation system. Therapeutic dose of vitamin K supplement to protect bone health in elderly women varies from 1.5 to as high as 45 mg/d, which is well tolerated.^{33,34} Nevertheless, therapeutic dosage for bone health still cannot ensure full carboxylation of osteocalcin. Although the doses of vitamin K supplement used in the studies included in the meta-analysis are far higher than dietary reference intake, varying from 500 $\mu\text{g}/\text{d}$ to 1.5 mg/d, it remains to be determined whether they are sufficient for improving insulin sensitivity. Oral supplementation of vitamin K1^{30–32,35,36} or vitamin K2^{33,34} was relatively nontoxic. Adverse events were only reported in one study in which falls, musculoskeletal side effects, and gastrointestinal disturbances were more common in subjects receiving vitamin K2 (MK-7) 100 $\mu\text{g}/\text{d}$ compared with placebo.³⁷ However, serious adverse events or death did not differ between the two groups.³⁷ Currently, the tolerable upper intake level of vitamin K has not been determined.

Our meta-analysis is not free from limitations. First, only published trials were included. Funnel plot and Egger's test were not conducted as the number of studies included in each meta-analysis was too small to permit reasonable use of those methods. Thus, publication bias cannot be ruled out. Secondly, the number of included studies was small. The estimates of effect may be imprecise. Substantial heterogeneity was detected in the meta-analysis of FPG,

adiponectin, and IL-6. Doses and forms of vitamin K varied from one trial to another. Subgroup analysis to separate the effect of vitamin K1 from vitamin K2 was not performed as the number of studies was too small. Characteristics of participants and variation in cointerventions may also have a role to play. In the analysis of fasting plasma glucose, for example, one trial included prediabetes premenopausal women,³² while the others enrolled postmenopausal women.^{30,31} Although these studies were aimed to evaluate the effect of vitamin K supplementation, some of them added multivitamin, vitamin D, and/or calcium to both the treatment and the control groups,^{30,31,35,36} while the others used vitamin K alone.^{32–34,37} It was therefore difficult to interpret the results and establish the sole effect of vitamin K supplementation.

Conclusion

In conclusion, this systematic review as well as meta-analysis suggests a lack of effect of vitamin K supplementation on insulin sensitivity. Given the limited evidence available and the heterogeneity in the study results, further well-designed, large sample size randomized controlled trials are warranted. Different forms and doses of vitamin K should be explored in various populations, and other surrogate markers for insulin sensitivity should be measured to better establish any beneficial effects and their clinical relevance.

Acknowledgment

This research was supported by grants from Thailand Research Fund (TRF) and Faculty of Pharmacy, Mahidol University, Thailand (IRG5780007).

Author contributions

NS and NP contributed to the design, analysis, and interpretation of data and drafted the manuscript. HDKK contributed to the conception, analysis, and interpretation of data and drafted the manuscript. All the authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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