Review

Beneficial role of vitamin K supplementation on insulin sensitivity, glucose metabolism, and the reduced risk of type 2 diabetes: A review

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Abstract

Micronutrients are gaining acceptance as an important nutritional therapy for the prevention and/or management of diabetes and its associated health risks. Although a very small quantity of micronutrients are required for specific functions in our bodies, moderate deficiencies can lead to serious health issues. Impaired insulin sensitivity and glucose intolerance play a major role in the development of diabetic pathophysiology. Vitamin K is well known for its function in blood coagulation. Moreover, several human studies reported the beneficial role of vitamin K supplementation in improving insulin sensitivity and glucose tolerance, preventing insulin resistance, and reducing the risk of type 2 diabetes (T2 D). Both animal and human studies have suggested that vitamin K-dependent protein (osteocalcin [OC]), regulation of adipokine levels, anti-inflammatory properties, and lipid-lowering effects may mediate the beneficial function of vitamin K in insulin sensitivity and glucose tolerance. This review for the first time provides an overview of the currently available preclinical and clinical evidences on the effect of vitamin K supplementation in the management of insulin sensitivity and glucose tolerance. The outcome of this review will increase understanding for the development of a novel adjuvant therapy to achieve better control of glycemia and improve the lives of diabetic patients.

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Introduction

Micronutrients have been increasingly used in various health care methodologies due to the realization of their importance in disease management [1,2]. In our body, micronutrients, generally coenzymes and/or cofactors for various metabolic reactions, are required for very specific functions. However, even moderate deficiencies can lead to serious health issues [1] (Fig. 1). Recent studies demonstrate the therapeutic potential of micronutrients for the prevention and/or management of many chronic diseases including diabetes [3–5]. Vitamin K is emerging as an important micronutrient for its beneficial role in improving insulin sensitivity and glucose metabolism and reducing the risk of type 2 diabetes (T2 D) [6–11].

Vitamin K, a fat soluble vitamin, is well known for its beneficial role in blood coagulation via functioning as a cofactor for γ-glutamate carboxylase in a posttranslational conversion of protein-bound glutamate residues into gamma carboxy glutamate (Gla) (Fig. 2) [12]. Phylloquinone (vitamin K1) and menaquinone (vitamin K2) are the two naturally occurring forms of vitamin K. Phylloquinone is the major dietary source of vitamin K and is found at highest concentrations in green leafy vegetables. However, significant concentrations of phylloquinone are also present in several vegetable oils, fruits, grains, and dairy products [13,14]. The major sources of menaquinone include meat, egg, curd, cheese, and fermented soybeans (natto). Many bacteria of the human intestine also synthesize menaquinone and utilize them as redox reagents in electron transport and oxidative phosphorylation; however, hardly any of them are absorbed because of the lack of bile salts at the site of production. It has also been observed that phylloquinone is converted into menaquinone-4 via integral side-chain removal [15]. This review for the first time provides an overview of the currently available preclinical and clinical evidences on the effect of vitamin K in the management of insulin sensitivity and glucose tolerance.

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Studies with dietary and supplemental phylloquinone (vitamin K1) intake on different measures on insulin sensitivity and glucose metabolism among various human populations

An earlier study by Sakamoto et al. (1999) reported a relationship between acute insulin response and phylloquinone intake among healthy young men (n = 16) after excluding low and high body mass index (BMI) subjects [16]. The daily phylloquinone intake was estimated using a one-week food checklist. It had been observed that low phylloquinone intake group had lower insulin and higher glucose concentrations (30 min after oral glucose loading) compared to high intake group. The insulinogenic index of the low phylloquinone intake group was also significantly lower than the high intake group. However, there was no association between phylloquinone intake and fasting glucose or insulin concentrations.

Later, Yoshida et al. (2008) examined the associations of self-reported phylloquinone intake with measures of both insulin sensitivity and glycemic status in a large community-based samples of men and women (1247 men and 1472 women, 26–81 y) recruited in Framingham Offspring Cohort [7]. Dietary and supplemental phylloquinone intakes for 12 mo were analyzed by using a semiquantitative food-frequency questionnaire (FFQ). Yoshida et al. also demonstrated that higher intake of phylloquinone was associated with greater insulin sensitivity, as measured by 2-h post oral glucose tolerance test (OGTT) insulin concentrations and the insulin sensitivity index (ISI0,120), and with better glycemic status, as measured by 2-h post-OGTT glucose concentrations, after adjustment for age, sex, waist circumference, lifestyle characteristics, and diet quality. The authors mentioned that delayed insulin release by the β-cells to oral glucose administration may explain the higher levels of 2-h post-OGTT insulin and glucose concentrations in persons with lower phylloquinone intake. However, this interpretation is limited because the study did not assess the effect of phylloquinone intake on the acute insulin and glucose responses to oral glucose loading. The associations between phylloquinone intake with those of fasting insulin and glucose concentrations, homeostasis model assessment of insulin resistance (HOMA-IR), or glycated hemoglobin were not observed.

In another study, Yoshida et al. (2008) also examined the effect of phylloquinone on the insulin resistance among older men and postmenopausal women (n = 355, 60% women, 60–80 y) population [8]. The dose of phylloquinone (500 µg/d, 36 mo) was approximately five times higher than the adequate intake [17]. Results suggest that HOMA-IR was significantly lower among men in the phylloquinone-supplemented group compared to the control group after adjustment for baseline HOMA-IR, BMI, and body weight changes. In addition, the beneficial effect of phylloquinone supplementation was also observed on the levels of fasting plasma glucose in the older men population. However, no significant differences in outcome measures were observed between the intervention group and respective controls in a female population. The percentage of overweight or obesity was higher among phylloquinone-supplemented women. Furthermore, an inverse association between plasma phylloquinone concentrations and BMI has been observed among women. Thus, the authors suggested that overweight or obesity, a major determinant of insulin resistance, might be the potential explanation for this lack of protective effect of vitamin K on insulin resistance in the population of women in that study. It was speculated that an increase in adipose tissue storage of fat-soluble vitamin K might inhibit the concentrations of the molecule available for peripheral organs.

The interpretation of these findings is limited by several factors. First, this study included an indirect measure of insulin resistance (i.e., HOMA-IR) instead of hyperinsulinemic-euglycemic clamp. Second, body composition was measured by BMI and percentage of body fat by dual energy x-ray absorptiometry, and neither provided information on regional adiposity. Third, this study was statistically underpowered. Finally, most of the participants were white.

The effect of phylloquinone supplementation on glucose metabolism had also been investigated by Kumar et al. among community-dwelling postmenopausal women (n = 21, ~60 y) [9]. Results showed that phylloquinone supplementation (1 mg/d, 12 mo) did not alter the levels of fasting glucose, insulin concentration, and HOMA-IR compared to control. There were certain limitations of this study. First, serum glucose and insulin concentrations were studied before and after the administration of phylloquinone, so it may be possible that the changes in the glucose disposition and insulin concentrations might have been present after an oral glucose load. Second, the study duration was 12 mo, and the changes in HOMA-IR might have occurred.

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Fig. 1. Micronutrient deficiency and its effect on health disorders.

Fig. 2. Vitamin K cycle. Vitamin K is functioning as a cofactor for the enzyme, γ-glutamate carboxylase (GGCX) which is essential for the conversion of glutamate (Glu) to γ-carboxylglutamate (Gla) residues of vitamin K-dependent (VKD) proteins. γ-Carboxylation transforms the undercarboxylated (ucVKD) into carboxylated (cVKD) VKD proteins.
over a longer period of time. Third, the increase in hepatic insulin clearance might have masked the increase in insulin secretion by the pancreatic β-cells.

Using the data from a prospective cohort study (38,094 Dutch men and women, ages 20–70 y), Beulens et al. investigated whether dietary phylloquinone intake is associated with a reduced risk of T2 D [10]. Dietary phylloquinone intakes were analyzed using an FFQ, and the intake was found to be \( \sim 200 \pm 98 \mu g/d \). Initially, it had been observed that in an age-, sex-, and waist-adjusted model, phylloquinone intake was not associated with reduced risk of T2 D for each 50 \( \mu g/d \) increment of phylloquinone intake. However, with adjustment for diabetes risk factors and dietary factors, phylloquinone intake was found to be associated \((P = 0.08)\) with reduced risk of T2 D and a hazard ratio \((HR)\) of \(0.81\) \((95\% CI: 0.66–0.99)\) for the highest versus lowest quartile. This association became non-significant again when modeled linearly per 50 \( \mu g \). A spline regression analysis also showed a nonlinear relationship between energy-adjusted phylloquinone intake and HR of T2 D \((P = 0.053)\). There are several strengths of this study, such as its prospective design, long follow-up, large sample size, and verification of T2 D by medical records. However, determination of phylloquinone intake by using FFQ is the main limitation of this study.

Recently Bullo et al. [11] reexamined the dietary phylloquinone intake and the risk of T2 DM among community-dwelling men \((aged 55–80 y)\) and women \((aged 60–80 y)\) \(\text{(out of a total of 2912 eligible candidates, 1925 subjects fulfilled the inclusion criteria and} \text{entered the Prevention with the Mediterranean Diet [PREDIMED] trial)}\) without cardiovascular disease but meeting at least one of the following two criteria: T2 D or \(\geq 3\) of the cardiovascular disease risk factors, such as smoking, hypertension, dyslipidemia, obesity, or a family history of premature cardiovascular disease. Dietary phylloquinone intake was analyzed by using an FFQ and the database of the United States Department of Agriculture. The median follow-up period was 5.5 y. Results demonstrated that at baseline there was no significant difference in the energy-adjusted intake of macronutrient between non-incident and incident TD subjects. However, energy-adjusted intake of phylloquinone was found to be lower \((P = 0.027)\) among incident T2D subjects \((285 \pm 131 \mu g/d)\) compared to non-incident subjects \((312 \pm 132 \mu g/d)\). Again, regression analysis in a model adjusted for potential confounders, such as age, sex, BMI, fasting glucose concentrations at baseline, total energy intake, intervention group, and smoking, showed that the baseline dietary phylloquinone intake was not associated with fasting plasma glucose concentrations at the end of follow up \((B = −0.615; 95\% CI: −1.531, 0.230)\), but, for each additional intake of 100 \( \mu g \) phylloquinone/d, the baseline dietary phylloquinone intake was associated with a 17% reduced risk of incident T2 D. Moreover, a 51% reduced risk of diabetes was also observed in subjects who increased the amount of dietary phylloquinone intake during the follow-up period compared to those who decreased or did not change the intake amount. The outcome of this study is in agreement with the earlier prospective cohort study conducted by Beulens et al. among Dutch subjects [10].

There are certain limitations of this study also. First, the findings of this study cannot be generalized to young and healthy individuals. Second, determination of phylloquinone intake by using an FFQ and United States Department of Agriculture food composition database included a slight overestimation of phylloquinone intake. Third, the subjects’ Mediterranean type diet may mask the beneficial effect of the increase in dietary phylloquinone intake on glucose metabolism and insulin sensitivity. However, the strength of this study includes longitudinal analysis that allowed the cause-effect relationship between dietary phylloquinone intake and the risk of developing T2 D and the repeated measurement of diet. In addition, the diagnosis of diabetes in this study was not self-reported and was verified by second analytical test.

The effect of vitamin K1 supplementation on insulin sensitivity and glycemic status has been reexamined by Rasekhi et al. among prediabetic and premenopausal women population \((22–45 y, BMI 18.5–30 kg/m^2)\) [6]. Results suggest that vitamin K1 supplementation \((n = 39, 1000 \mu g/d, 4 \text{wk})\) caused a significant decrease in fasting glucose, 2-h post-OGTT glucose and insulin concentrations, and an increase in insulin sensitivity index, but did not affect the insulin resistance \((\text{HOMA-IR)}\) compared to placebo \((n = 43)\). The authors suggested that dosage and intervention duration of vitamin K1 may affect insulin resistance as this pathophysiological condition has occurred over a longer period of time. Table 1 represents a review about the effect of phylloquinone on the different measures of insulin sensitivity, glucose metabolism, and the reduced risk of T2 D among human subjects.

### Studies with menaquinone (vitamin K2) intake on insulin sensitivity and the reduced risk of T2 D among different human populations

Most of the study of vitamin K on insulin sensitivity and glucose homeostasis includes phylloquinone. Few studies have investigated the effect of menaquinone (vitamin K2) on insulin sensitivity and glucose metabolism. Choi et al. (2011) for the first time demonstrated a direct effect of menatetrenone \((30 mg, 4 \text{wk})\) on an increase in insulin sensitivity among healthy young men \((n = 18, \text{ages} 25.5–31.5 y)\) compared to placebo \((n = 15, \text{ages} 24–31 y)\) [19]. Results showed that vitamin K2 supplementation significantly increased insulin sensitivity index \((4.4 \text{versus} 6.6)\) and disposition index \((2441 \text{versus} 4835)\) before and after treatment, but these effects were not observed in placebo-treated group, which suggests a beneficial role of vitamin K2 on improved glucose intolerance. The small sample size of this study limits any firm interpretations regarding the beneficial effect of vitamin K2 on insulin secretion and glucose homeostasis.

Beulens et al. (2010) also examined the beneficial effect of dietary menaquinone intake against the risk of type 2 diabetes by using the data from a cohort study \((38,094 \text{Dutch men and women, ages} 20–70 y)\) [10]. Dietary menaquinone intake \((31 \pm 7 \mu g/d)\) was analyzed using an FFQ. Results showed that menaquinone intake was inversely associated \((P = 0.060)\) with the risk of T2 D with an HR of 0.95 \((95\% CI: 0.91–1.01)\) in an age, sex, and waist-adjusted model. A multivariate model showed the same inverse relationship \((P = 0.038)\) with an HR of 0.93 \((0.87–1.00)\) for each 10-µg increment of menaquinone intake. Spline regression analysis again demonstrated a linear inverse relationship between energy-adjusted menaquinone intake and the risk of T2 D \((P = 0.035)\). This study demonstrated a beneficial role of menaquinone with a reduced risk of T2 D. A brief summary about the effect of menaquinone on the different measures of insulin sensitivity, glucose metabolism, and the reduced risk of T2 D among human subjects has been demonstrated in Table 1.

### Studies with vitamin K and the prevalence of metabolic syndrome (MetS)

Pan and Jackson demonstrated a relationship between dietary phylloquinone intake and MetS by performing a cross-sectional analysis on data from 5800 American adults \((\text{aged} 20–45 y)\)
who participated in the National Health and Nutrition Examination Survey (NHANES) 1999–2004 [18]. Participants with MetS were classified if they had three or more of the following conditions: 1) hyperglycemia (fasting glucose level ≥100 mg/dL), 2) hypertriglyceridemia (triacylglycerols ≥150 mg/dL), 3) lower high-density lipoprotein (HDL) level (<40 mg/dL in men or <50 mg/dL in women), 4) higher blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg), and 5) waist obesity (waist circumference >102 cm in men or >88 cm in women). Dietary phylloquinone intake data were calculated using a standard questionnaire from a 24-h dietary recall: 85.8 μg/d for males and 83.8 μg/d for females. In general, participants with MetS consumed less phylloquinone from diet compared to those who did not. Results demonstrated the lowest prevalence of MetS and its five components among individuals with the highest phylloquinone intake. Among the five components of MetS, an increase in dietary phylloquinone intake was significantly associated with a decrease in the prevalence of elevated blood pressure and reduced HDL cholesterol (P < 0.05).

The association between the dietary intake and/or status of vitamin K with MetS and its components has also been reexamined by Dam et al. [20]. This study examined data of two cohort studies, one comprised 402 women (49–70 y) from the PROSPECT study [21] and another comprised 400 men (40–80 y) [22]. Dietary phylloquinone and menaquinene intakes were calculated using a FFQ, and the serum vitamin K status was estimated by dp-ucMGP concentration instead of the individual levels of the different forms of vitamin K. Since vitamin K is well known for the activation of γ-gluatmate, carboxylase in a posttranslational conversion of protein-bound glutamate residues into gamma carboxy glutamate. Thus measurement of the plasma levels of dp-ucMGP appears to be a marker for the overall plasma vitamin K status [23,24]. This study also used the same components of MetS as defined in the previous study [18]. The mean phylloquinone and menaquinene intakes were 210.3 ± 127.0 μg/d and 31.1 ± 12.5 μg/d, respectively. The serum vitamin K status as estimated by dp-ucMGP concentration was 299.6 ± 344.8 pM.

Higher menaquinone intake was associated with a lower prevalence of MetS (P_{trend} = 0.08, borderline significant after full adjustment and P_{trend} = 0.05 when BMI was excluded as confounder) for the highest versus lowest tertile. Longitudinal analyses also demonstrated the significant association between the menaquinone intake with the lowest prevalence of MetS (P_{trend} = 0.01) in a fully adjusted model for the highest versus lowest tertile, and this association remained unchanged even after the exclusion of BMI. Both the cross-sectional analysis and longitudinal analyses showed that dietary phylloquinone intake was not associated with the lower prevalence of MetS. Again, elevated serum vitamin K status was associated with a reduced prevalence of MetS in a fully adjusted model (P_{trend} = 0.01), but this relation changed slightly when BMI was excluded. In this study, the relation of menaquinone intake with MetS was mainly driven by an association with triacylglycerol concentration and lower waist circumference for the association of vitamin K status with MetS.

### Vitamin K and diabetic animal studies

Limited animal studies examined the role of vitamin K on glucose metabolism. Varsha et al. demonstrated the beneficial role of phylloquinone against streptozotocin (STZ)-induced type 1 diabetes in male albino Wistar rats [25]. Phylloquinone administration (5, 25, and 50 mg/kg body weight [bw], 2.5 mo, subcutaneously) decreased the free radicals formation and restored the antioxidant enzymes activities in the pancreatic tissues of the STZ-treated rats. Phylloquinone treatment rescued the pancreatic cell death, increased the islet area, and enhanced the insulin secretion followed by normoglycemia and lower glycosylated hemoglobin levels in diabetic rats. Immunohistochemical studies showed the function of phylloquinone in suppressing NF-κB activation and inducible nitric oxide synthase expression in the islets of STZ-treated rats. This suggests a beneficial role of phylloquinone in preventing the activation of proinflammatory genes and islet oxidative stress. Varsha et al. also observed that phylloquinone treatment

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**Table 1**

<table>
<thead>
<tr>
<th>Subjects/duration of the study</th>
<th>Form of vitamin K (Effective dose)</th>
<th>Outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 1247) and women (n = 1472), ages 26–81 y/12 mo of follow up (Framingham Offspring Cohort)</td>
<td>Dietary phylloquinone intake (ranged from 10–1975 μg/d)</td>
<td>Greater insulin sensitivity and better glycemic status.</td>
<td>[7]</td>
</tr>
<tr>
<td>Men and women (n = 355, 60% women, ages 60–80 y)/36 mo supplementation</td>
<td>Phylloquinone supplementation (500 μg/d)</td>
<td>Lowered insulin resistance and fasting glucose among men.</td>
<td>[8]</td>
</tr>
<tr>
<td>Postmenopausal women (n = 21, aged ≥ 60 y)/12 mo supplementation</td>
<td>Phylloquinone supplementation (1 mg/d)</td>
<td>No change in fasting glucose, insulin concentrations, and insulin resistance.</td>
<td>[9]</td>
</tr>
<tr>
<td>Men and women (n = 38,094), 20–70 y/10.3 y of follow up (Prospective Cohort)</td>
<td>Dietary phylloquinone intake (200 ± 98 μg/d)</td>
<td>Reduced risk of T2 DM.</td>
<td>[10]</td>
</tr>
<tr>
<td>Men and women (n = 1925, 55–80 y)/5.5 y of median follow up (PREDIMED trial)</td>
<td>Dietary phylloquinone intake (316 ± 141 μg/d)</td>
<td>Reduced risk of T2 DM.</td>
<td>[11]</td>
</tr>
<tr>
<td>Prediabetic and premenopause women (n = 39, ages 22–45 y)/4 wk supplementation</td>
<td>Phylloquinone supplementation (1000 μg/d)</td>
<td>Decreased fasting glucose, 2-h post-OGTT glucose and insulin concentrations, and increased insulin sensitivity index.</td>
<td>[6]</td>
</tr>
<tr>
<td>American adults (n = 5800, ages 20–45 y)/6 y of follow up (NHANES 1999–2004)</td>
<td>Dietary phylloquinone intake (84.8 ± 3.2 μg/d)</td>
<td>Lower prevalence of MetS and its components.</td>
<td>[18]</td>
</tr>
<tr>
<td>Young men (n = 18, ages 25.5–31.5 y)/4 wk supplementation</td>
<td>Menatetrenone (30 mg/d)</td>
<td>Increased insulin sensitivity index and disposition index.</td>
<td>[19]</td>
</tr>
<tr>
<td>Men and women (n = 38,094), 20–70 y/10.3 y of follow up (prospective cohort)</td>
<td>Dietary menaquinene intake/31.7 μg/d</td>
<td>Reduced risk of T2 DM.</td>
<td>[10]</td>
</tr>
<tr>
<td>Women (n = 402, ages 49–70 y) (PROSPECT study) and men (n = 400, ages 40–80 y)</td>
<td>Dietary intakes of phylloquinone (210.3 ± 127.0 μg/d) and menaquinone (31.1 ± 12.5 μg/d)</td>
<td>Lowered MetS in menaquinene intake group. No association in phylloquinone-intake group.</td>
<td>[20]</td>
</tr>
</tbody>
</table>
(subcutaneously, 5 mg/kg bw, twice a week) reduced the cataract formation in the STZ-treated rat via regulating the blood glucose homeostasis and minimizing the subsequent oxidative and osmotic stress [26]. These studies suggest a beneficial role of phylloquinone in regulating glucose homeostasis in STZ-treated diabetic animals.

The beneficial effect of vitamin K2 on glucose homeostasis has also been investigated by Iwamoto et al. using STZ-treated diabetic male Sprague-Dawley rats [27]. Vitamin K2 (menatetrenone) was administered by oral gavaging (30 mg/kg bw, five times a week, 12 wk). Results demonstrated that menatetrenone administration prevented the development of hyperglycemia in STZ-treated rats. In addition, menatetrenone also showed its beneficial effect on cancellous bone mass in STZ-treated diabetic rats. However, this study did not examine the molecular mechanism underlying the beneficial role of menatetrenone on STZ-induced hyperglycemia in rats.

Both of the animal studies used STZ-induced type 1 diabetic rats to examine the beneficial effect of vitamin K against diabetes. STZ is a well-known drug commonly used to induce experimental model of type 1 diabetes [28]. STZ administration causes a significant pancreatic beta cell death, decreases insulin production, and induces the pathogenesis of hyperglycemia [28]. Thus, it may be speculated that to combat the toxic effect of STZ and also to reduce the pancreatic beta cell death, the merit of vitamin K in STZ-induced diabetic rats was observed after treatment for a long time.

Khalil et al. (2014) recently examined the protective role of vitamin K2 against impaired glucose homeostasis in ovariectomized exercised and non-exercised rats [29]. Vitamin K2 supplementation (menaquinone-7, 0.0009 mg/kg bw/d, 9 wk) decreased the glucose levels and increased the insulin, lipocalcin-2, and adiponectin levels in both ovariectomized exercised and non-exercised rats compared to those seen in only ovariectomized rats. This suggests a beneficial role of vitamin K2 on insulin sensitivity and glucose metabolism.

Possible mechanisms

Role of vitamin K dependent protein, OC in insulin sensitivity and glucose metabolism

Molecular mechanisms underlying the beneficial role of vitamin K on insulin sensitivity and glucose homeostasis have not been resolved yet. Various studies in the literature reported the role of vitamin K-dependent protein, OC in the regulation of glucose metabolism [30]. OC is one of the most abundant non-collagen bone matrix proteins and regulates the size and shape of hydroxyapatite via its γ-carboxylated form [30]. Vitamin K stimulates the γ-carboxylation of Gla residues of OC and thereby mediates the strong binding of OC to hydroxyapatite. Total OC concentration includes both carboxylated OC and under-carboxylated OC (ucOC). The percentage of ucOC decreases in response to vitamin K supplementation and increased due to vitamin K depletion [30]. Various animal studies including both knockout and wild type models reported the function of OC in improving β-cell proliferation, insulin expression and its secretion, and adiponectin expression in adipocytes, which suggests a role of OC in regulating glucose metabolism by improving β-cell function and insulin sensitivity [31,32]. Several epidemiologic studies also reported the negative association between OC levels with BMI, fat mass, blood glucose, insulin concentrations, and insulin resistance [33,34]. However, the form of OC that is involved in the regulation of glucose metabolism has not been yet been determined.

Using genetically modified mice, Lee et al. showed the role of ucOC in regulating glucose metabolism and fat mass [31]. Ferron et al. also reported the role of ucOC in improving glucose tolerance via stimulating the expression of insulin and adiponectin in wild-type mice [32]. However various clinical studies reported that serum total OC concentrations (not the undercarboxylated form) are inversely associated with the measures of glucose metabolism, such as fasting plasma glucose, insulin, HOMA index, and so on [6,33–35]. Interestingly, vitamin K intake, which causes a decrease in the concentration of ucOC, has been reported to reduce insulin resistance among patients at high risk of T2 D [6,8,9,19,36], which is opposite to what would be expected from the animal studies. Thus, there is an inconsistency between the human evidences and the experimental models regarding the nature of OC involvement in glucose metabolism.

The possible reasons could be speculated as follows

First, the genetic difference between mice and human could be one of the possible reasons. Humans have only one OC gene, whereas mice have three. In mice, about 60% of protein sequences are conserved compared with humans [30,37]. In addition, OC gene in humans is upregulated by vitamin D: in mice, however, the gene is downregulated [30,37]. Second, the knockout mouse model has a total lack of OC, whereas in humans, the levels may vary but not completely absent [30,37]. Third, the serum OC levels in humans shows diurnal variation, and it is increased during ageing, growth and skeletal maturation, and menopause [38,39]. Fourth, the concentration of ucOC in human includes two different consequences: suboptimal vitamin K intake and the osteoclast activity and matrix acidification [30,40]. However, most of the human studies do not take into account vitamin K concentrations or intake and the independent measures of bone formation and resorption during the assessment of the link between ucOC and glucose metabolism [30,40]. Fifth, the concentrations of human OC in bone and the circulatory system are only 20% of those seen in other species and that is also incompletely carboxylated [30]. Finally, there are still some limitations in the measurement of OC and its carboxylated and undercarboxylated form, and thus the interpretation could bias the results [41,42]. Therefore, further studies are required to define the nature of OC involving in the regulation of glucose metabolism.

Effect of vitamin K on circulating adipokines’ levels

Changes in the circulating levels of adipocyte-derived factors, adipokines, play an important role in insulin resistance [43–45]. Bullo et al. examined the effect of dietary phylloquinone intake on adipokines and other risk markers related to insulin resistance and diabetes among elderly participants (n = 510, 67.2 ± 6 y, 44.4% male) recruited in the PREDIMED trial [46]. In cross-sectional analyses at baseline, after adjusting for potential confounders, a significant negative association was observed between dietary phylloquinone intake and plasma PAI-1 concentration, but not with the other metabolic risk markers. However, after 1-year follow-up, subjects who increased their dietary intake of phylloquinone showed a significant (P < 0.05) reduction in inflammatory cytokines, such as leptin (–10.3%), tumor necrosis factor (TNF) (–26.9%), interleukin (IL)-6 (–27.9%), and other metabolic risk factors related to insulin resistance and diabetes, like, ghrelin (–15%), glucagon-like peptide-1 (–17.6%),
visfatin (−24.9%), and glucose-dependent insulinotropic peptide (−12.9%), compared to those who decreased or did not change the intake amount. These results could explain the beneficial role of phylloquinone in the regulation of insulin sensitivity and glucose homeostasis. The limitation of this study performed by Bullo et al. includes the same parameters as in their previous study mentioned previously [11].

Adiponectin, another well-known adipokine is also a positive regulator of insulin sensitivity [47]. Rasekhi et al. reported that dietary phylloquinone supplementation (1000 μg/d, 4 wk, premenopausal women, 22–45 y) significantly increased the adiponectin concentrations and decreased the 2-h post-OGTT glucose and insulin concentrations compared to placebo [48]. However, adjustments for total OC and adiponectin did not affect the association of glycemic status with related variables. This suggests that the beneficial effect of phylloquinone on improved glycemic status in premenopausal prediabetic women is independent of adiponectin. Kanpen et al. again observed that vitamin K2 supplementation also did not affect circulating adiponectin concentrations among healthy men and postmenopausal women [49]. Further studies are necessary to examine the role of vitamin K on adiponectin levels.

Antiinflammatory role of vitamin K

TNF-α and IL-6 are the most widely studied proinflammatory cytokines causing insulin resistance [50,51]. Ohsaki et al. demonstrated that vitamin K1 supplementation decreased the IL-6 mRNA expression in lipopolysaccharide-treated THP-1 cells [52]. Reddi et al. also demonstrated that treatment with both vitamin K1 and vitamin K2 prevented the IL-6 production in lipopolysaccharide-stimulated human gingival fibroblasts [53]. A recent study by Shea et al. has demonstrated an inverse relationship between the vitamin K status and the circulating measures of inflammation [54]. Results suggested that poor vitamin K status was associated with high concentration of cytokines, IL-6, and C-reactive protein. Beulens et al. also showed an inverse relationship between dietary menaquinone intake and the levels of high sensitive C-reactive protein [10]. The mechanism underlying the beneficial role of vitamin K against the production of proinflammatory cytokines is unclear. However, it has been suggested that vitamin K may regulate NF-κB activation and thus inhibit the production of proinflammatory cytokines [52]. More specifically, Varsha et al. showed that administration of vitamin K1 downregulates NF-κB activation in the islet tissue of STZ-treated type 1 diabetic rats [25]. Upon activation, NF-κB induces the secretion of various proinflammatory molecules, such as TNF-α, monocyte chemotactic protein 1, IL-6, and other [55]. The inhibitory influence of vitamin K on NF-κB may lead to a decrease in the expression of IL-6 and other cytokines. A detailed study about the influence of different doses and forms of vitamin K on inflammatory cytokine production will dissect the antiinflammatory role of vitamin K.

Lipid-lowering efficacy of vitamin K

Elevated total cholesterol and low-density lipoprotein cholesterol and reduced HDL cholesterol are associated with insulin resistance and impaired glucose metabolism [56]. Recent studies reported the important role of vitamin K in the regulation of dyslipidemia [57,58]. Kawashima et al. reported that vitamin K2 supplementation reduced the plasma levels of total cholesterol in hypercholesterolemic rabbits [57]. In addition, Kawashima et al. observed that vitamin K2 treatment delayed the progression of atherosclerotic plaque formation, intima-thickening, and pulmonary atherosclerosis. In line with this finding, Sogabe et al. also observed that supplementation of both vitamins K1 and K2 (menaquinone-4) significantly decreased the total fat accumulation and serum triacylglycerol levels by 48% and 29%, respectively, compared to control diet–fed rats [58]. The lipid lowering effect of vitamin K2 has also been observed among patients on continuous ambulatory peritoneal dialysis [59]. On the contrary, Kolahi et al. reported that vitamin K1 has no effect on the lipid profile in women with rheumatoid arthritis [60]. Thus, the function of vitamin K1 on plasma lipid profile has not been resolved yet and needs further investigation.

Conclusion

Based upon the studies in this review, it has been observed that intakes of both naturally occurring forms of vitamin K, phylloquinone and menaquinones, are beneficial among a cohort of patients with MetS and a high risk of T2D. For phylloquinone intake, these risk reductions occurred at higher levels of intake; however, in the case of menaquinones, the level of intake was low for the same risk reductions. In addition, it has been suggested that menaquinone is more effective in activating extrahepatic vitamin K–dependent proteins than phylloquinone [61]. These studies suggested that menaquinone could be more effective than phylloquinone in reducing the risk of T2D.

At present there is no recommended dietary allowance for vitamin K. Across geographic regions and age groups, wide ranges of vitamin K intakes have been observed [62]. The adequate intake (AI) of a nutrient is defined as the median level, which is supposed to be the adequate amount based upon the observation of groups of apparently healthy people. The AI values for phylloquinone intake have been estimated from the US Third Nutrition and Health Examination Survey (NHANES III), and the established amount is 120 μg/d for men and 90 μg/d for women [17]. For menaquinones, the estimated AI values are 54 μg/d for men and 36 μg/d for women, based upon the data from the UK National Dietary and Nutrition Survey [63]. In this review, some studies included higher doses of phylloquinone [6,8,9]; however, there is so far no adverse effect associated with either phylloquinone or menaquinones reported in the literature, including both animal and clinical studies. The Institute of Medicine at the US National Academy of Sciences (NHANES III) (1988–1994) has also indicated there is no documented case of toxicity in humans or animals associated with the consumption phylloquinone or menaquinone from food or supplements [17].

The interpretation of this review is limited by several factors. First, this study did not separate the effect of dietary vitamin K intake with those seen in vitamin K supplementation. The calculation of dietary vitamin K intakes using an FFQ is the major limitation for many studies. Second, this review did not dissect the effect of different forms of menaquinones on the various measures of glucose metabolism.

This review for the first time provides an overview of the currently available preclinical and clinical evidence about the beneficial role vitamin K supplementation on insulin sensitivity and glucose metabolism, which may be helpful for the development of a novel adjuvant therapy to achieve better control of glycemia and improve the lives of the diabetic patient population. Overall, it has been suggested that carboxylation of vitamin K-dependent protein, regulation of adipokine secretion, antiinflammatory property, and lipid lowering effect may mediate the beneficial function of vitamin K in insulin sensitivity and glucose tolerance (Fig. 3). However, there is so far no
mechanistic study describing in detail about the molecular mechanism underlying the beneficial role of vitamin K in insulin sensitivity and glucose metabolism. Thus, future studies with diabetic animals and diabetic patients are needed to dissect the molecular mechanism underlying the beneficial function of vitamin K in improving insulin sensitivity and glucose metabolism in diabetic pathophysiology.

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