REVIEW

POSSIBLE BENEFICIAL EFFECTS OF VITAMIN K AND OSTEOCALCIN ON GLUCOSE METABOLISM

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ABSTRACT

The role of vitamin K, in bone metabolism and its effects on insulin resistance and Type-2 diabetes, have been discussed. The mechanism of vitamin K's beneficial effect on insulin sensitivity and glucose homeostasis is not yet known. Various biological active molecules such as adiponectin, leptin, and resistin, which is secreted from adipose tissue and have important roles in glucose metabolism, have been proposed to regulate bone metabolism. Some studies have suggested that bone metabolism is also effective on adipose tissue and energy metabolism. It is thought that osteocalcin, a vitamin K dependent protein is effective in glucose metabolism. The role of Vitamin K in glucose metabolism is thought to be partly due to the modulation of diabetes-related cytokines and other metabolic risk markers, as inflammation lies at the bottom of chronic metabolic diseases. The aim of this review is to explain the effect of Vitamin K and osteocalcin on glucose metabolism and its possible mechanisms of action.

Keywords: Vitamin K, osteocalcin, glucose metabolism, type 2 diabetes, insulin resistance

INTRODUCTION

Micronutrients have been received as a supplement to health promotion and disease prevention after recognizing their important role in the management of diseases (1). Even moderate deficiencies of micronutrients, which usually act as coenzymes or cofactors in metabolic activities in our bodies, cause serious health problems (1, 2). In recent years, it has been determined that micronutrients have a therapeutic effect on many chronic diseases including diabetes (3, 4).

The crucial role of Vitamin K in blood coagulation is well known (5). Carl Peter Henrik Dam (6) who discovered Vitamin K, to symbolize its ability to coagulate, named the vitamin as "K". Vitamin K has two natural forms: phylloquinone (Vitamin K1) and menaquinone (Vitamin K2) (2, 7). Phylloquinone, the most important form of dietary Vitamin K, is found in many vegetable oils, fruits, dairy products, and cereals as well as green vegetables (2). While the most important sources of menaquinone in dietary intake are meat, cheese, and eggs, it is mainly produced by intestinal bacteria (8). Besides, phylloquinone can be converted to menaquinone-4 (9). Furthermore, vitamin K functions as a cofactor for γ-glutamyl carboxylase enzyme which is essential for the vitamin K dependent proteins (9).

Previous studies have focused on the role of Vitamin K in blood coagulation (5, 6). Besides its role in blood coagulation, Vitamin K improves bone health, prevents vascular calcification, and reduces the risk of cardiovascular diseases (10–12). Furthermore, it is considered to have beneficial effects against insulin resistance (13). Recent studies have shown that Vitamin K increases insulin sensitivity, improves glucose metabolism, and reduces the risk of Type-2 diabetes mellitus (14–18). In a study conducted by Ertaş-Öztürk et al. (19) Vitamin K and glucose metabolism of non-obese healthy individuals were investigated. It is determined that dietary Vitamin K intake may have a protective effect on insulin resistance. However, another study showed that glucose tolerance was not improved by seven days of Vitamin K supplementation (20). The association between Vitamin K and Type-2 diabetes mellitus and the way it possibly uses to prevent insulin resistance are unclear. This review aims to explain the effect of Vitamin K on Type-2 diabetes mellitus and its potential mechanisms.

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The Relationship Between Glucose Metabolism and Vitamin K

Diet and lifestyle play an important role in the progression of insulin resistance, a metabolic disorder in which hepatic and peripheral tissues are less susceptible to insulin (21). In recent years, there have been studies proposing that Vitamin K intake or deficiency was related to insulin resistance (14–16). The mechanism of vitamin K on insulin sensitivity and glucose homeostasis are not yet known (2). Various biological active molecules such as adiponectin, leptin and, resistin (22-24), which are secreted from adipose tissue and have important roles in glucose metabolism, have been proposed to regulate bone metabolism. Some studies have suggested that bone metabolism is effective on adipose tissue and energy metabolism (25, 26). Many studies have suggested that osteocalcin which is a vitamin K dependent protein, is effective in regulating glucose metabolism (9, 15, 25). It has been determined that osteocalcin stimulates β-cell proliferation, insulin secretion, and insulin sensitivity by stimulating adiponectin secretion (25).

Bone and glucose metabolism are linked by a complex metabolism that contains leptin, osteocalcin, and adiponectin (27). The possible effects of Vitamin K intake and osteocalcin on glucose metabolism are shown in Figure 1.

Osteocalcin is a Vitamin-K dependent protein synthesized by osteoblasts (7). It has been thought that osteocalcin is the most common non-collagen protein in the bone and its concentration is positively correlated with osteoblast function and Vitamin K availability (12). Vitamin K acts as the cofactor of the gamma-glutamyl carboxylase enzyme which is essential for the synthesis of osteocalcin (Figure 2). Osteocalcin contains a propeptide recognition site for binding gamma-carboxyglutamate (13). After carboxylation, the propeptide is separated and active osteocalcin is synthesized (28). Gamma-carboxyglutamate residues in the osteocalcin are responsible for the shape, size, and bone metabolism of the bone mineral (7, 10).

Studies have described three forms of osteocalcin: carboxylated, uncarboxylated and undercarboxylated osteocalcin (7). The difference between uncarboxylated and undercarboxylated osteocalcin has not yet been clearly explained. However, it has generally been reported that high serum undercarboxylated or uncarboxylated osteocalcin is associated with the low levels of Vitamin K (10). Although changes in the concentration of undercarboxylated osteocalcin have been reported not to affect glucose metabolism, many researchers have reported that the active form of osteocalcin is undercarboxylated (7, 27). It was reported that Vitamin K supplementation (K1 or K2) decreased the level of non-carboxylated osteocalcin, increased the level of carboxylated osteocalcin, and reduced insulin resistance in patients with the high risk of Type-2 diabetes (10). As a result of a study of 348 non-diabetic men and women for three years, Shea et al. (29) reported that uncarboxylated osteocalcin was not associated with higher insulin resistance whereas low carboxylated osteocalcin was associated with higher insulin resistance. However, Hwang et al. (30) suggested that both carboxylated and non-carboxylated osteocalcin levels improved glucose tolerance.

Lee et al. (31) investigated the endocrine regulation of energy metabolism by the skeleton. In that study, the osteocalcin gene was inactivated in mice. Visceral fat accumulation was impaired and the hyperglycemic state and impaired glucose tolerances were due to insulin resistance and insulin deficiency. It was found that osteocalcin increased beta-cell proliferation, insulin release, and sensitivity by stimulating insulin and adiponectin in beta-cells and adipocytes. Mice that could not produce osteocalcin were found to be obese, had low beta-cell proliferation, and developed insulin resistance (31). In another study, Vitamin K2 supplementation at different doses in rats during 8 weeks period increased the expression of osteocalcin, insulin 1, insulin 2, cyclin D2, which are the indicators of B-cell proliferation (32). Some amino acids and sizes of osteocalcin in mice and humans are different (27, 33). The roles of osteocalcin in glucose metabolism in in-vitro and in-vivo studies should be supported with human studies. Human and animal studies should be examined together to make a general conclusion. Table 1 summarizes human and animal studies investigating the effects of vitamin K and/or osteocalcin on glucose metabolism.

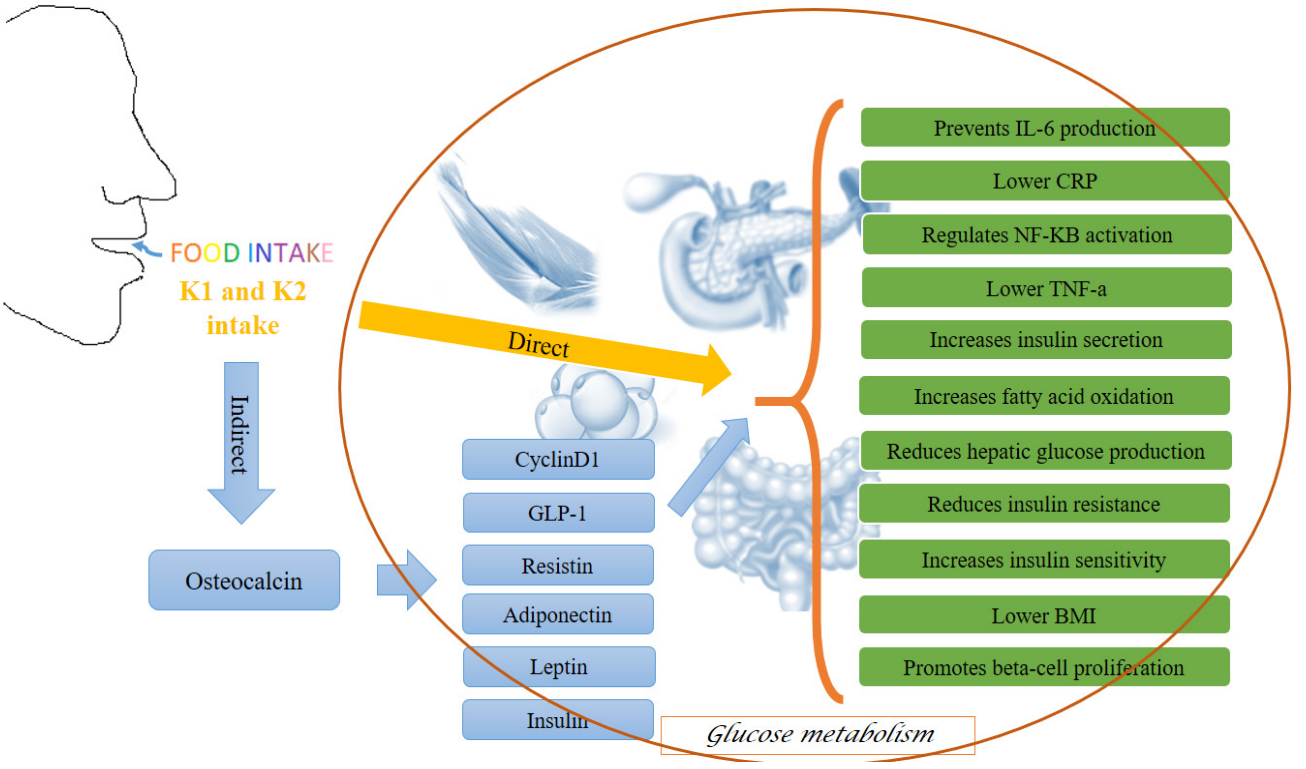

Figure 1: Possible direct and indirect mechanisms of Vitamin K and osteocalcin on glucose metabolism.

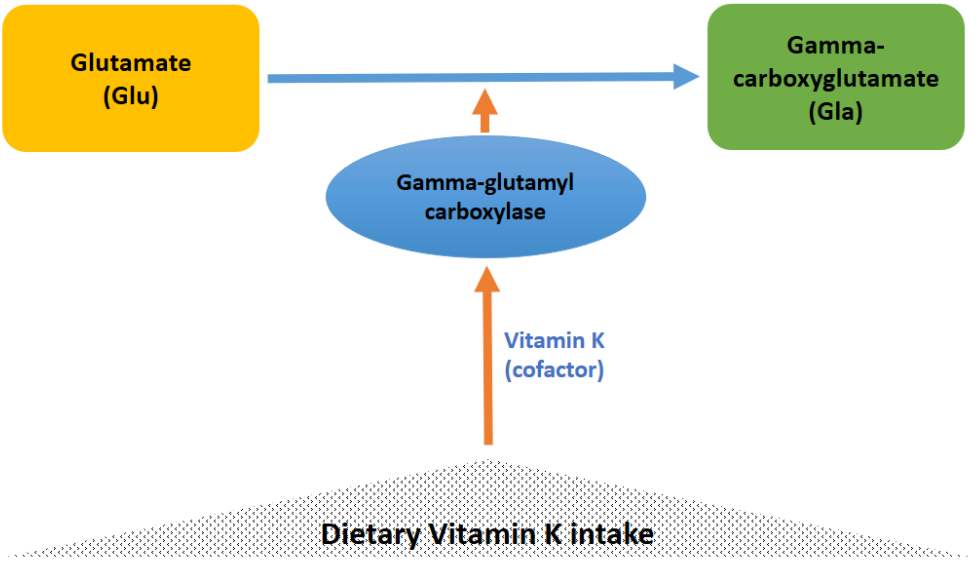

Figure 2: Vitamin K is a cofactor for gamma-glutamyl carboxylase.

Table 1: Effects of Vitamin K and/or osteocalcin on glucose metabolism.

Study	Participants and design	Outcomes
Beulens et al. (14)	The levels of intake of Vitamin K1 and Vitamin K2 were evaluated by food frequency questionnaire which was questioned for the last 1 year of 38 094 Dutch men and women aged 21-64 years.	Each 10-mcg increment of menaquinone intake was associated with a 7% decrease in the risk of Type 2 diabetes.
Ibarrola-Jurado et al. (15)	2353 male diets were followed for a mean of 5.5 years.	The dietary intake of phylloquinone every 100 mcg/day was associated with a 17% lower incidence of diabetes.
Kumar et al. (16)	During postmenopausal period, 1 mg/day phylloquinone supplementation was performed for 12 months.	There was no significant difference in fasting blood glucose, insulin concentration and HOMA-IR levels in the control group.
Rasekhi et al. (17)	In a randomized controlled study of 82 prediabetic women supplemented with Vitamin K1 for 4 weeks.	According to the control group, fasting blood glucose and insulin concentration were lower in patients who received supplemental treatment, but insulin resistance (HOMA-IR) was not affected.
Yoshida et al. (18)	Dietary Vitamin K intake of 2719 individuals was evaluated by the food frequency questionnaire.	Higher phylloquinone intake was determined to have higher insulin sensitivity and better glycemic control.
Saleem et al. (26)	Serum osteocalcin levels of 1209 white people and 1284 black people were measured.	There was a relationship between serum osteocalcin levels and BMI, fasting blood glucose, insulin resistance, leptin, and adiponectin levels, which had a statistically significant difference.
Shea et al. (29)	348 non-diabetic individuals were followed for three years.	Higher levels of carboxylated osteocalcin were associated with lower fasting blood glucose, insulin resistance, and higher adiponectin levels.
Hwang et al. (30)	Serum osteocalcin levels of 199 men were measured.	Increased levels of both carboxylated and non-carboxylated osteocalcin were found to improve glucose tolerance in patients with impaired glucose tolerance.
Hussein et al. (32)	Vitamin K2 supplementation was performed at different doses to 30 rats for 8 weeks.	Osteocalcin, insulin 1, insulin 2, Cyclin D2 expressions were determined to increase.
Sakamato et al. (34)	Dietary Vitamin K intakes of individuals were determined by food frequency questionnaire.	The group receiving low dietary phylloquinone intake had lower insulin and higher blood glucose concentration.
Yoshida et al. (35)	In a randomized, double-blind controlled study, the elderly and non-diabetic 355 individuals underwent phylloquinone supplementation for 36 months.	HOMA-IR levels were found to be lower in the elderly than in the control group.
Pittas et al. (36)	Serum osteocalcin levels of 380 individuals over 65 years of age were measured.	Serum osteocalcin concentration was strongly correlated with plasma fasting glucose, insulin resistance, IL-6, body mass index (BMI) and body fat.
Pollock et al. (37)	Osteocalcin levels of 140 overweight prepubertal children with prediabetes and normal glucose levels were measured.	Low osteocalcin levels were found to be related to B-cell dysfunction in children with prediabetes.
Asemi et al. (38)	Vitamin D, Vitamin K and calcium (Ca) were supplemented to 66 diabetic patients.	Insulin concentrations, insulin resistance (HOMA-IR) and β-cell function were significantly different from the placebo group.
Choi et al. (39)	Menakinon-4 supplements were administered to 42 healthy adults.	In the K2-supplemented group, the level of carboxylated osteocalcin increased and insulin sensitivity improved compared to the placebo group.
Juanola-Falgarona et al. (40)	Dietary Vitamin K intake of 510 elderly people was followed for a year.	Diabetes-related inflammatory cytokines in those who increase dietary intake of Vitamin K decreased.
Varsha et al. (41)	Rats with Type-1 DM were supplemented with Vitamin K1 twice a week for 3 months.	Activation of proinflammatory genes and beta-islet necrosis were prevented. Beta-cell proliferation is facilitated.
Liang et al. (42)	1049 non-diabetic and 983 participants followed for four years.	People with impaired glucose metabolism have low osteocalcin level.

In epidemiological studies, dietary or supplementary intake of Vitamin K has been shown to reduce insulin resistance and improve glycemic levels (29, 34, 36, 37). Sakamoto et al. (34) evaluated the insulin responses depending on the intake of Vitamin K in the diet of participants who have normal body weight. It was determined that the group receiving low phylloquinone had lower insulin and higher blood glucose concentration. In a study conducted by Beulens et al. (14), each 10-mcg increase of menaquinone intake with diet was associated with a 7% reduction in the risk of Type-2 diabetes. The effect of vitamin K on glucose metabolism has often been associated with osteocalcin.

Low osteocalcin level is a risk factor for impaired glucose metabolism and Type-2 diabetes (42). However, in a study, no correlation was found between osteocalcin and glucose levels in patients with normal glucose tolerance (35). These studies demonstrate that the level of osteocalcin is closely related to glucose metabolism.

In a study performed by Saleem et al. (26), a significant relationship was found between serum osteocalcin levels and BMI, fasting blood glucose, insulin resistance, leptin, and adiponectin levels. Another study on older people showed that serum osteocalcin levels were associated with glucose metabolism, serum osteocalcin concentration was strongly correlated with plasma fasting glucose, insulin resistance, IL-6, body mass index and body fat (36). Pollock et al. (37) reported that osteocalcin is associated with glucose metabolism, and this relationship is associated with beta-cell functions. This study was conducted on prepubertal children. Although these studies focused on different age groups, the results were found to be compatible with each other.
Not only cross-sectional studies, but also longitudinal studies showed that Vitamin K and osteocalcin were effective in glucose metabolism. In a long-term follow-up study, dietary intake of 100 mcg/day was associated with a 17% lower incidence of diabetes (15). In another follow-up study showed that low osteocalcin level was associated with impaired glucose metabolism (42). The strong relationship between vitamin K, osteocalcin, and glucose metabolism has been supported by these longitudinal studies.

Studies evaluating dietary vitamin K intake have shown beneficial effects on glucose metabolism. In addition to dietary intake, there are studies evaluating vitamin K intake as a supplement. In a recent study, 66 diabetic patients received Vitamin D, Vitamin K, and calcium supplementation. In this randomized, double-blind, placebo-controlled study, it was determined that insulin concentrations, insulin resistance (HOMA-IR) and β-cell function showed significant differences compared to the placebo group (38). Choi et al. (39) evaluated insulin sensitivity by giving menaquinone-4 supplements to healthy young men for 4 weeks. It was determined that the level of osteocalcin and insulin sensitivity were higher than the placebo group in the supplemented group.

Since various forms of vitamin K are used, these studies are open to interpretation. In Rasekhi et al.'s study (17) Vitamin K1 supplementation was given to prediabetic women for 4 weeks. According to the control group, the fasting blood glucose levels and the insulin concentration were lower but the insulin resistance (HOMA-IR) was not affected. In another study conducted on 21 women during the postmenopausal period, 1 mg/day phylloquinone supplementation was given for 12 months. However, there was no significant difference in fasting blood glucose, insulin concentration, and HOMA-IR levels compared to the control group (16). In that study, although supplementation was performed for a longer period, it was not effective on insulin resistance, which is accepted as the initial stage of diabetes mellitus (16). In a recent meta-analysis, similarly, it was reported that Vitamin K supplementation does not affect insulin sensitivity (43). The lack of beneficial effects of these results on glucose metabolism as much as dietary intake suggests that the synthetic form of vitamin K may be ineffective.

It has been reported that studies supplementing animals may be useful in contradiction to human studies. Intraperitoneal undercarboxylated osteocalcin injection is known to affect glucose metabolism by increasing insulin secretion (44). In a study by Mizokami et al. (45), it was stated that GLP-1, one of the incretin hormones, increased the secretion of insulin by increasing intraperitoneal undercarboxylated osteocalcin injection in mice.

The Relationship Between Inflammation and Vitamin K

The role of Vitamin K in glucose metabolism is thought to be partly due to the modulation of diabetes-related cytokines and other metabolic risk markers (40). In addition, inflammation lies at the bottom of chronic metabolic diseases (46). Vitamin K causes a decrease in free radicals as a potential antioxidant (47). In vitro studies have shown that Vitamin K decreases the production of proinflammatory cytokines (40, 48, 49). Although it is not known how Vitamin K affects inflammation biomarkers, it is thought to suppress inflammation by decreasing the gene expression of cy-

tokines such as IL-6 (48). Additionally, it is known to have a protective effect against oxidative stress (50).

In a study on type-1 diabetic rats, Vitamin K1 treatment inhibited Nuclear Factor Kappa B (NF-KB) activation. This treatment is thought to possibly prevent beta-islet necrosis, favor beta-cell proliferation/regeneration, increase insulin production, and decrease hyperglycemia. Therefore, it is thought that Vitamin K1 supplementation may be beneficial for the complications of diabetes, not only for Type-1 diabetes, but also for beta-cell damage (41). It has been determined that the expression of genes involved in the acute inflammatory response is increased in Vitamin K deficient rats (48). Additionally, phylloquinone was found out to inhibit the activation of pro-inflammatory genes and prevent oxidative stress (41). In a study conducted on 1381 individuals, low plasma phylloquinone levels were associated with high pro-inflammatory markers (CRP and IL-6) (46).

In a study conducted on 379 healthy subjects, at three years follow up, it was determined that subjects with high cytokine concentration were associated with inadequate dietary Vitamin K (29). However, there was no significant difference in the concentration of cytokines such as IL-6 and CRP in individuals receiving phylloquinone supplementation (29). In a study conducted by Juanola-Falgarona et al. (40) on 510 people, the relationship between dietary Vitamin K intake and insulin-related peripheral adipokines and other metabolic risk markers related to Type-2 diabetes were investigated. It was determined that inflammatory cytokines such as leptin, tumor necrosis factor (TNF), interleukin (IL) -6 as well as other metabolic risk factors such as ghrelin, glucagon-like peptide-1, and visfatin were significantly decreased in the elderly who increased their phylloquinone intake for a year.

Reasons For Inconsistencies In The Studies

Human and animal osteocalcin genes differ from each other (33). The Vitamin K-associated osteocalcin gene is upregulated in humans with Vitamin D while it is downregulated in mice (33). Also, some amino acids and the levels of osteocalcin in mice and humans are different (27, 33). These differences seen in human and animal studies are attributed to serum osteocalcin level with age, growth, access to skeletal maturity and changes in day to day with menopause (51). In humans, non-carboxylated osteocalcin may occur as a result of decarboxylation during optimal Vitamin K uptake or osteoclast absorption (10). This situation may also cause contradictions. The food frequency questionnaires used in epidemiological studies were not sensitive enough to differentiate the phylloquinone and menaquinone intake. The reasons for the inconsistency of the results of the studies are thought to be the differences in the distribution and metabolism of menaquinone and phylloquinone in the body. In addition to sufficient positive effects of vitamin K taken as a supplement on people's glucose metabolism have not been observed.

CONCLUSION

The role of Vitamin K and osteocalcin on glucose metabolism and its possible mechanisms of action have been discussed in this review. Although the mechanism of action is not clearly understood, Vitamin K has been shown to reduce the risk of insulin resistance. It is thought that especially the menaquinone form prevents Type-2 diabetes. Despite the fact that there are many in vivo studies performed in mice, further human studies are required on this subject.

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