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Original Research Article

The Importance of Vitamin K in Type 2 Diabetes Mellitus: A Comprehensive Review

Varsha Shirur[1], Bhavya Vats[2], Simran Manjrekar[3], Aarya Vidhate[4], Deepali Vidhate[5]

[1]Assistant Professor Department of Biochemistry, D. Y. Patil Deemed to be University school of Medicine. Nerul, Navi Mumbai.

[2]MBBS students D. Y. Patil deemed to be University school of Medicine. Nerul, Navi Mumbai.

[3]Junior resident, Department of Biochemistry, D. Y. Patil Deemed to be University school of Medicine. Nerul, Navi Mumbai.

[4]MBBS intern D. Y. Patil deemed to be University school of Medicine. Nerul, Navi Mumbai.

[5]Professor and H.O.D. Department of Biochemistry, D.Y. Patil Deemed to be University school of Medicine. Nerul, Navi Mumbai

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Corresponding author: Dr. Varsha Shirur

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Abstract

Vitamin K, which includes phylloquinone (K1) and menaquinones (K2), has been recognized as a potentially important micronutrient in relation to diabetes mellitus. In addition to its well-known function in blood coagulation, vitamin K plays a role in glucose metabolism and insulin sensitivity through the activation of osteocalcin and the regulation of matrix Gla protein. Research indicates that a deficiency in vitamin K may lead to reduced insulin secretion and heightened insulin resistance, which could worsen complications associated with diabetes. Additionally, the anti-inflammatory and antioxidant effects of vitamin K may provide protective benefits against vascular damage linked to high blood sugar levels. Therefore, exploring the therapeutic potential of vitamin K supplementation to slow the progression and complications of diabetes mellitus is an area that requires further in-depth clinical research.

Keywords: Vitamin K, Diabetes mellitus, Insulin sensitivity, Glucose metabolism, Osteocalcin, interleukin, inflammation.

Introduction

Vitamin K is a fat-soluble vitamin that plays a crucial role in the functionality of various proteins in the body, including coagulation factors (II, VII, IX, X, along with protein C and protein S), osteocalcin (a protein essential for bone formation), and matrix-Gla protein (MGP), which helps prevent calcification and has impact on glucose metabolism [1-2].

Vit k is a cofactor for enzyme γ-glutamyl carboxylase, carboxylation in endoplasmic reticulum is dependent on vit which affects ca binding Store-operated Ca^{2+} entry (SOCE) mechanism, which regulates glucose stimulated insulin secretion in beta cells. Endoplasmic reticulum Gla protein resist SOCE channels to prevent overfilling of Ca in beta cells which causes beta cell dysfunction which is vitk dependent [3]. This vitamin is available in two natural forms: vitamin K1 (phylloquinone) and vitamin K2 (menaquinone, ranging from MK-4 to MK-10)[2-5]. Vitamin K1 is predominantly found in green leafy vegetables, as well as in olive oil and soybean oil, while vitamin K2 is present in smaller quantities in foods such as chicken, butter, egg yolks, cheese, and fermented soybeans, commonly referred to as natto[2,6-9]

Enhancement of insulin sensitivity and glucose regulation –

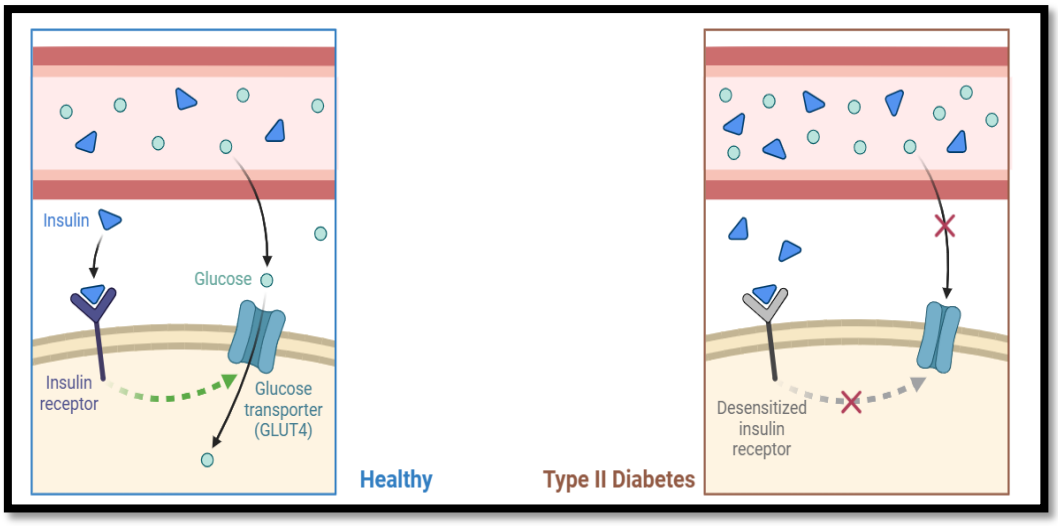


Figure 1: Healthy Condition and Type – II Diabetic Condition

Numerous studies have investigated the impact of vitamin K on insulin response and glycaemic control. The findings suggest a positive correlation between blood Vitamin K levels and plasma insulin concentrations, while fasting plasma glucose levels remained relatively stable with Vitamin K consumption. Observational research indicated that, 30 minutes post-glucose loading, plasma glucose levels showed a tendency to decrease, and the insulinogenic index increased among individuals with high Vitamin K intake, implying that Vitamin K may enhance acute insulin response and improve glucose tolerance [10].

Additionally, a study focusing on older adults found that greater Vitamin K1 consumption was associated with improved insulin sensitivity and glycaemic control during a 2-hour oral glucose tolerance test, indicating potential benefits of Vitamin K1 for glucose homeostasis in both men and women [11].

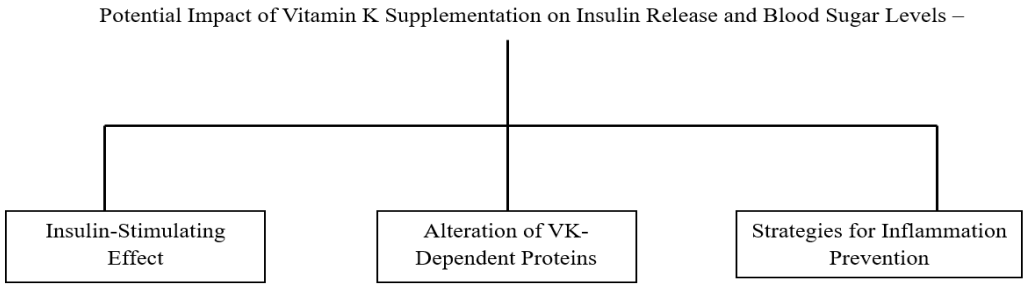
Conversely, men with lower Vitamin K1 intake exhibited reduced insulin levels and elevated glucose levels compared to those with higher Vitamin K1 intake [12,13]. A recent Mendelian randomization study revealed that elevated circulating Vitamin K1 levels are linked to a decreased risk of type 2 diabetes mellitus (T2DM) [14]. In intervention trials, a long-term study on Vitamin K supplementation in older nondiabetic individuals demonstrated that after 36 months, insulin resistance improved in older men but not in women [15,16]. More recent intervention studies also reported that a four-week Vitamin K1 supplementation enhanced glycaemic control and insulin sensitivity in premenopausal and prediabetic women [16].

In contrast, one week of Vitamin K2 intake significantly lowered the immunoreactive insulin/plasma glucose ratio following oral glucose loading [17,18]. Another research group corroborated these findings, showing that four weeks of Vitamin K2 supplementation increased insulin sensitivity in healthy young men[19]. In studies involving animals, rats that had a low intake of vitamin K exhibited a diminished early insulin response and experienced late hyperinsulinemia following an intravenous glucose tolerance test.

Additionally, in a rat model of arteriosclerosis with diabetes mellitus, the combined treatment of vitamin K2 (MK-4) and oestradiol led to a reduction in aortic calcium and phosphorus levels, as well as a decrease in serum glucose levels, while simultaneously increasing serum insulin levels. This combination therapy was effective in slowing the progression of arteriosclerosis associated with diabetes [20,21].

Table 1: Human Studies and Animal Studies with respect to Vitamin K and Type – II Diabetes

Sr No	Number of Subjects	Period Dose of Vitamin K	Period	Outcome	Reference
Human Studies					
1	Healthy young males.	Standard dietary consumption.	Acute insulin response A food-frequency questionnaire conducted over one week to determine the daily intake of VK.	Participants who consumed higher levels of dietary VK demonstrated improved insulin response and enhanced glucose tolerance.	[18]
2	Framingham offspring cohort research, adult males and females.	Standard dietary consumption.	12 Months	A cross-sectional study found that increased dietary intake of vitamin K was linked to lower insulin resistance in both adult males and females.	[11]
3	Older males and females with elevated cardiovascular risk.	Standard dietary consumption.	The average follow-up period was 5.5 years.	Dietary VK1 levels at baseline were notably lower in participants who went on to develop T2DM during the study. An increase in dietary VK1 consumption was linked to a decreased risk of developing incident T2DM.	[13]
4	Older nondiabetic males and females.	With or without the supplementation of 500 μg/day of VK1.	36 Months	Dietary supplementation with VK1 demonstrated a protective influence on the advancement of insulin resistance among older men.	[15]
5	Women with prediabetes.	VK1 supplementation at a dosage of 1000 μg/day, regardless of its presence or absence.	4 Weeks	Dietary supplementation with VK1 positively influenced glycaemic control and enhanced insulin sensitivity in premenopausal women who are prediabetic.	[16,17]
Animal Studies					
1	Rats	Low-VK diet (less than 20% of the necessary VK1 intake).	Not Known	Rats that were given a low-VK diet exhibited a weak initial insulin response, which was followed by a heightened insulin secretion in reaction to a glucose challenge.	[20]
2	Arteriosclerotic rat model exhibiting diabetes mellitus.	100 mg of VK2 per kilogram of body weight daily.	3 Weeks 6 Weeks	VK2 supplementation demonstrated a protective role against arteriosclerosis by reducing aortic calcium and phosphorus levels, as well as the elastin fraction. Rats that were given a diet high in VK2 exhibited lower serum glucose levels and elevated serum insulin levels.	[21]



Alteration of VK-

Dependent Proteins - Vitamin K (VK) serves as a cofactor for microsomal γ-glutamyl carboxylase and is essential for the posttranslational carboxylation of glutamate to γ-carboxyglutamate (Gla) residues in VK-dependent proteins (VKDPs), including matrix Gla protein (MGP) and osteocalcin (OC). These proteins are significant in preventing vascular calcification and regulating bone mineralization, respectively [22,23,24,25]. Additionally, VKDPs contribute to various biological processes and the regulation of physiological functions. Research has indicated a link between the status of VKDPs and disease progression, implying that VKDPs could serve as potential biomarkers for a range of diseases. Furthermore, Vitamin K status may be particularly important in conditions such as diabetes mellitus [26]. Active matrix Gla protein (MGP) is acknowledged as a vascular calcification inhibitor, both in laboratory settings and in living organisms, and is regarded as a biomarker for vitamin K deficiency. [27-30].

Inactive MGP exists in various forms, including carboxylated or phosphorylated variants, such as uncarboxylated MGP (ucMGP), carboxylated but not phosphorylated MGP (dpcMGP), phosphorylated but uncarboxylated MGP (pucMGP), and the fully inactive uncarboxylated, dephosphorylated MGP (dpucMGP)[31,32]. Numerous studies have indicated that medial calcification occurs in patients with diabetes mellitus (DM), which is associated with the presence of vitamin K-dependent proteins (VKDPs)[33-39]. An initial study reported that medial calcification was more prevalent in DM patients compared to those without diabetes [34]. Additional research has shown that the buildup of advanced glycation end products is linked to coronary artery calcification in individuals with type 1 diabetes mellitus (T1DM)[35], and those suffering from severe aortic valve stenosis.[32]. Moreover, elevated levels of ucMGP have been observed in DM patients,[36,39],suggesting a heightened risk of arterial calcification, which has also been noted in non-diabetic individuals and patients with type 2 diabetes mellitus (T2DM)[36,37,38].

Strategies for Inflammation Prevention – Previous research studies has showed that vitamin K can inhibit interleukin IL-6 production in models of lipopolysaccharide-induced inflammation. [40,41]. Additionally, higher plasma levels and intake of VK1 have been correlated with lower levels of inflammatory markers TNF-α and IL-6[42]. Other studies have also indicated that the reduction of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 in adipose tissue, is linked to improved insulin sensitivity.[43-45]. Obesity is known to induce a state of low-grade inflammation, which plays a significant role in the onset of insulin resistance and type 2 diabetes mellitus (T2DM).

This suggests that elevated levels of proinflammatory cytokines are crucial mediators of innate inflammatory responses that lead to insulin resistance. [46-48]. additionally, various chronic diseases associated with inflammatory disorders have been linked to vitamin K (VK) deficiency [49-51]. Evidence suggests that VK may help improve insulin response and glycaemic control by reducing inflammation. A study examining fat-soluble vitamin levels in patients with chronic pancreatitis found that these individuals had lower serum concentrations of fat-soluble vitamins and reduced bone mineral density [51].

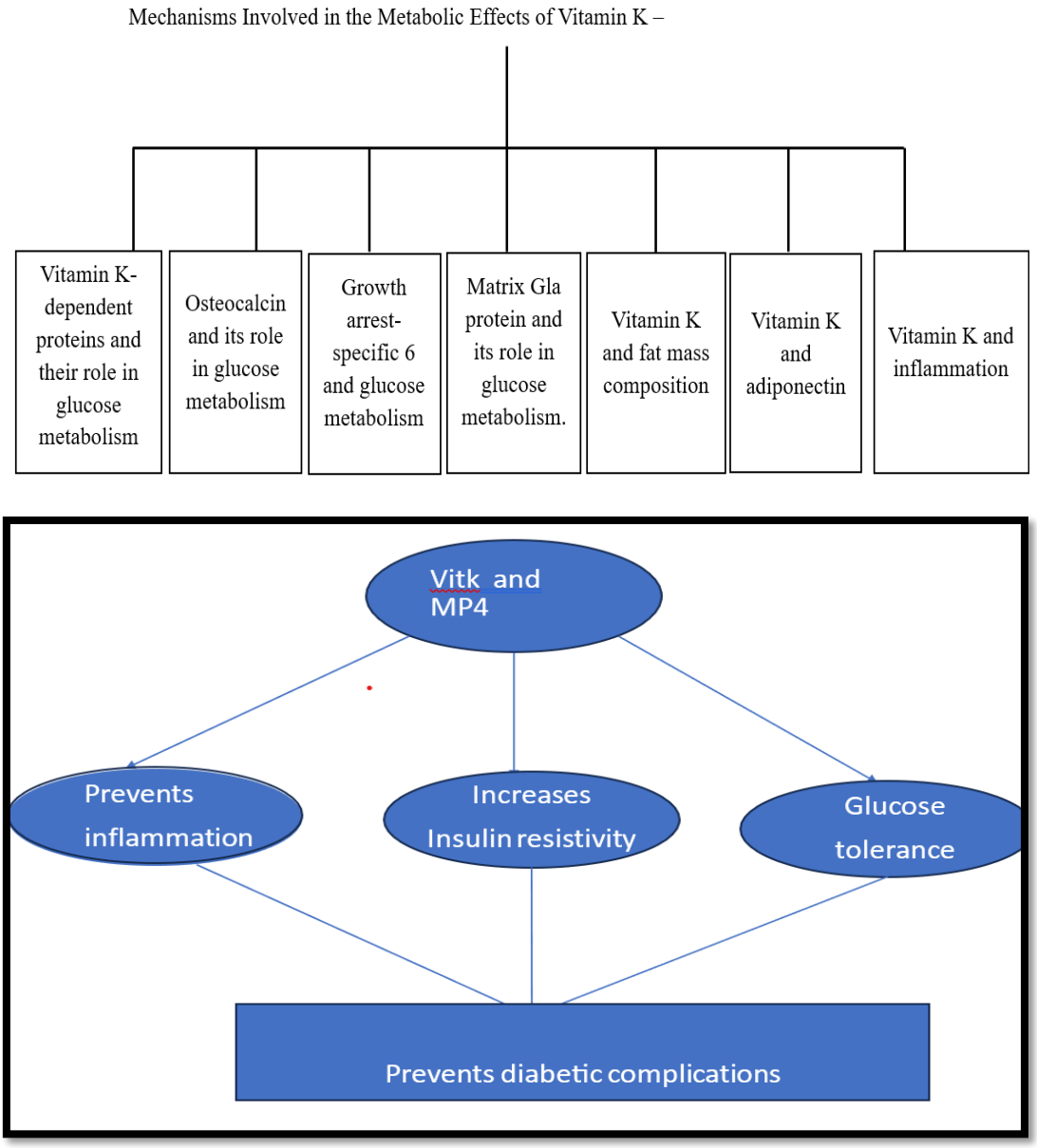


Figure 2: Role of Vit k in insulin sensitivity

Vitamin K-dependent proteins and their role in glucose metabolism- Vitamin K facilitates the maturation of proteins known as Gla proteins through a process called gamma-carboxylation, which is primarily mediated by the enzyme gamma-glutamyl carboxylase. Osteocalcin, growth arrest-specific 6 protein (Gas6), and Matrix Gla protein (MGP) are among the most extensively researched Gla proteins in the context of metabolism. The levels of uncarboxylated and carboxylated forms of these proteins show an inverse and positive correlation, respectively, with vitamin K status. Study showed that plasma Gas6 levels lowered in impaired glucose metabolism in typ2 diabets patients [52].

Osteocalcin and its role in glucose metabolism - Osteocalcin is a crucial no collagenous protein found in the bone matrix. There are varying findings regarding the metabolic role of osteocalcin in relation to its carboxylation status. Some studies, both in vitro and in vivo, indicate that g-carboxylation of osteocalcin may negatively influence its endocrine function.[53-55].

Conversely, the metabolic activity of uncarboxylated osteocalcin appears to be influenced by sex, with differing effects observed in male and female mice [56]. Additionally, research has demonstrated that carboxylated osteocalcin correlates with insulin resistance and glucose intolerance in nondiabetic overweight and obese postmenopausal women. Furthermore, vitamin K may enhance insulin sensitivity in adult male rats by elevating total osteocalcin levels in a dose-dependent manner [58]. Recent studies involving postmenopausal women have also identified an inverse relationship between total

osteocalcin levels and the incidence of type 2 diabetes [53-59].

The technical intricacies involved in assessing the carboxylation status of osteocalcin, along with the influence of various potential confounders such as age, sex, estrogen levels, dietary factors, and bone mineral density, may account for the discrepancies observed in the findings of these studies. Nonetheless, vitamin K may influence glucose metabolism by affecting either the carboxylation status or the overall levels of osteocalcin. Research focused on the metabolic impacts of osteocalcin should consider the ratios of carboxylated to uncarboxylated osteocalcin, as well as the ratio of uncarboxylated to total osteocalcin, rather than relying solely on the concentrations of different osteocalcin forms [55].

Growth arrest-specific 6 and glucose metabolism - Gas6 is a Gla-protein that serves as a receptor ligand for the TAM (Tyro3, Axl, MerTK) family of receptor tyrosine kinases. It is secreted by various immune cells and is involved in several biological processes, including the release of proinflammatory cytokines, the differentiation of natural killer cells, and the development of adipocytes [60]. Type 2 diabetes is characterized by chronic low-grade inflammation, and given Gas6's role in inflammatory processes, there is increasing interest in its potential impact on glucose metabolism. Research indicates that plasma Gas6 levels are associated with visceral obesity in women (showing a negative correlation with waist circumference), insulin sensitivity (negatively correlated with HOMA-IR and positively correlated with the insulin sensitivity index and quantitative insulin sensitivity check index), and inflammation (negatively correlated with interleukin-6 and positively correlated with TNF-α)[61]. Although genetic variants of Gas6 do not correlate with elevated circulating levels of the protein, they are linked to insulin resistance and diabetic status in Asian patient cohorts [62,63]. Nevertheless, prospective studies have not established a predictive relationship between Gas6 and the development of type 2 diabetes [62].

Matrix Gla protein and its role in glucose metabolism - A further focus of vitamin K dependent protein is matrix Gla protein (MGP). Recent research has identified a notable positive linear relationship between MGP levels and both homeostasis model assessment equation (HOMA-IR) and insulin levels [64]. Currently, there is a lack of additional data regarding the connection between MGP and glucose metabolism.

Vitamin K and fat mass composition - Waist circumference is closely linked to visceral fat, which is significantly associated with insulin resistance. A notable reduction in abdominal fat and visceral fat was observed following vitamin K2 supplementation (180 mg of menaquinone-7 daily) when compared to the placebo group and those with minimal response [65]. Additionally, a higher vitamin K status, as indicated by carboxylated MGP levels, was correlated with a significantly smaller waist circumference in women,[66]. According to a cross-sectional study. In a longitudinal analysis, a marginally significant relationship was identified between vitamin K status and waist circumference in men exclusively [66].

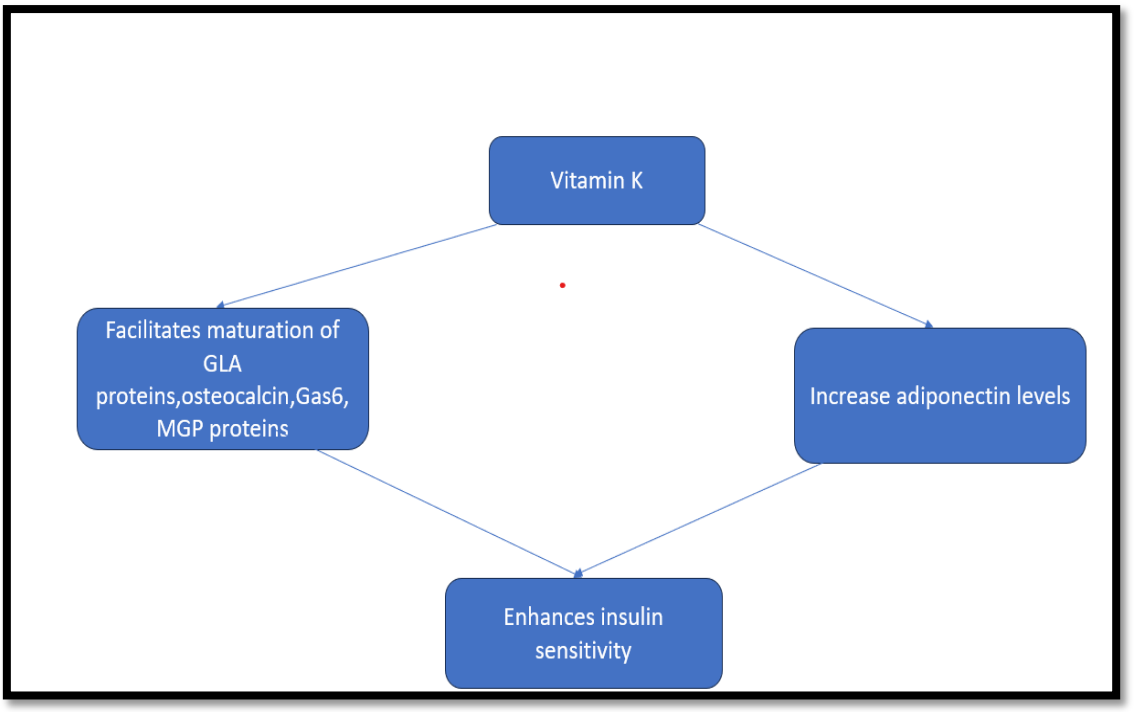


Figure 3: Effect of vit K on proteins and Adiponectin

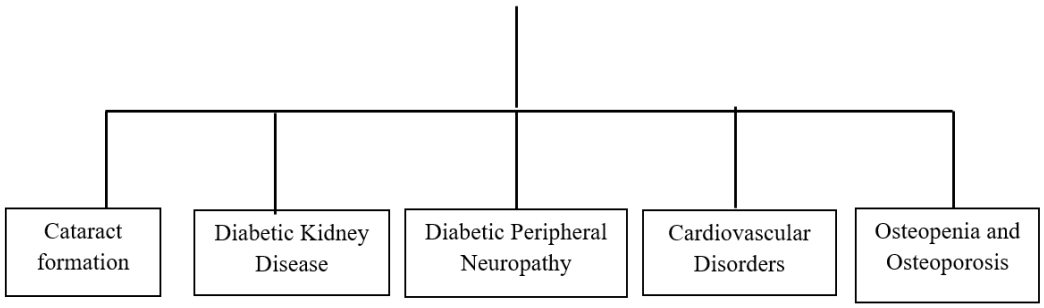
Vitamin K and adiponectin – Adiponectin is essential in the context of insulin resistance. Initial studies indicated that vitamin K supplementation was linked to an increase in total adiponectin plasma levels [67]. However, findings from this study reveal that the enhancement of glycaemic control following vitamin K supplementation occurred independently of adiponectin levels. A recent meta-analysis indicates that vitamin K supplementation does not influence total adiponectin concentration [68]. Nonetheless, this analysis overlooks recent evidence demonstrating that vitamin K supplementation can significantly elevate both total and high molecular weight adiponectin in circulation [65].

Vitamin K and inflammation - Previous research has indicated a potential inhibitory role of vitamin K in inflammation; however, a recent meta-analysis found no significant impact of vitamin K supplementation on either C reactive protein (CRP) levels or circulating IL-6[69]. Conversely, a recent in-vitro study demonstrated that vitamin K1 supplementation influences inflammation by reducing NF-kB phosphorylation (Nuclear Factor) and the secretion of Monocyte Chemoattractant Protein-1. [70].

This anti-inflammatory effect appears to be associated with the activation of vitamin K-dependent Gla proteins.

The advantages of vitamin K in addressing complications associated with diabetes - The global prevalence of diabetes mellitus (DM) associated with metabolic complications is on the rise. Complications related to diabetes are typically categorized into microvascular and macrovascular issues, which encompass conditions such as retinopathy, kidney disease, neuropathy, and cardiovascular disease (CVD) [71,72].

Diabetic complications:



Cataract formation - A recent investigation revealed that vitamin K-dependent protein (VKDP), specifically active matrix Gla-protein (MGP), possesses properties that prevent calcification and stiffness, thereby supporting retinal microcirculation, which may serve as an indicator of retinal health [73]. In a model of STZ-induced diabetes in rats, cataract development was associated with hyperglycaemia, elevated lens aldose reductase 2 (ALR2) activity, sorbitol accumulation, and the production of advanced glycation end products in the eye lens, contributing to cataract formation related to diabetes. Conversely, rats treated with VK1 showed reductions in blood glucose levels, ALR2 activity, and lens sorbitol accumulation. The findings suggest that VK1 effectively inhibits ALR2 by targeting its substrate-binding site, indicating a potential mechanism by which VK1 may influence the development of diabetes-related cataracts [74,75].

Diabetic Kidney Disease - There is a growing body of evidence indicating that diabetic nephropathy represents a significant complication associated with both Type 1 and Type 2 diabetes mellitus. Numerous studies have highlighted the prevalence of inadequate vitamin K (VK) status and, consequently, reduced serum levels of vitamin K-dependent proteins (VKDPs) in individuals suffering from chronic kidney disease (CKD)[76-80]. Specifically, the level of matrix Gla-protein (MGP), a VKDP, has shown a strong correlation with the stages of CKD. An inverse relationship has been observed between circulating levels of dephosphorylated uncarboxylated MGP (dpucMGP) and CKD stages, suggesting that MGP may serve as a prognostic marker for mortality in patients with diabetic nephropathy [80,81]. Additionally, plasma levels of dpucMGP have been linked to albuminuria and proteinuria, while also demonstrating an inverse association with estimated glomerular filtration rate (eGFR) [82,83]. Patients with CKD undergoing maintenance haemodialysis exhibited elevated plasma dpucMGP levels [84,85,86]. Furthermore, cohort studies have indicated that plasma dpucMGP levels tend to rise with the advancement of CKD, particularly in those classified within CKD Stages 3 to 5 [86,87]. Other research has explored the implications of increasing dpucMGP levels on renal function, noting that an increase in the renal resistive index (RRI), a common measure of renal dysfunction, correlates with negative renal and cardiovascular outcomes [88]. A recent investigation found that dpucMGP levels were associated with renal resistive index (RRI), cardiovascular risk factors, and renal function [89].

Additionally, findings from the Nephrotic Syndrome Study Network cohort revealed that renal MGP expression was elevated in rats subjected to 5/6 nephrectomy [90]. This study also examined the relationship between MGP levels and kidney biopsy data, revealing that eGFR was inversely related to the expression of MGP mRNA in both tubulointerstitial and glomerular tissues in nephrotic syndrome patients. Notably, tubulointerstitial MGP mRNA expression was significantly associated with renal inflammation, fibrosis, and acute tubular injury, independent of eGFR levels.

Elevated levels of MGP mRNA expression were linked to a heightened risk of experiencing a 40% reduction in eGFR and the onset of end-stage renal disease [90]. This finding underscores the protective role of MGP in renal health and suggests that vitamin K has a positive impact on kidney function.

Diabetic Peripheral Neuropathy - Diabetic peripheral neuropathy represents a common and serious metabolic complication associated with diabetes mellitus (DM). Poor glycaemic control and dyslipidemia are recognized as significant risk factors for the development of diabetic neuropathy [91,92]. Research indicates a potential link between vitamin K (VK) status and the maintenance of nervous system homeostasis. An earlier study highlighted VK's role in promoting the survival of central nervous system (CNS) neurons [93]. Additionally, it has been reported that matrix Gla protein (MGP) is expressed in both neurons and glial cells [94].

The early differentiation and growth of neurons, along with dendrite formation, the maturation of Schwann cells, and myelination, are influenced by the interactions between the extracellular matrix and MGP [95-97]. Furthermore, elevated levels of dpucMGP in the plasma of patients with diabetic peripheral neuropathy and inadequate VK status suggest that MGP is involved in maintaining nervous system homeostasis [38]. Diabetic neuropathy is often accompanied by comorbidities such as retinopathy and nephropathy. Other studies have indicated that VK may have a Reno protective effect, which could also help in preventing additional complications related to diabetes.

Cardiovascular Disorders – A prevalent complication among individuals with diabetes mellitus (DM) is cardiovascular disease (CVD), which encompasses conditions such as heart failure, vascular disease, and stroke [98].

In a study involving an arteriosclerotic rat model with DM, the administration of MK-4 alongside oestradiol was found to lower the levels of calcium and phosphorus in the aorta, thereby inhibiting the advancement of arteriosclerosis associated with DM [21]. Additionally, inadequate vitamin K (VK)

status has been linked to a heightened risk of CVD in patients suffering from DM [37].

A proof-of-concept study involved patients with aortic valve calcification and normal renal function, who were assigned to either the VK1 or placebo groups for a duration of 12 months. The findings revealed that VK administration led to a reduction in serum dpucMGP levels and decelerated the progression of cardiac valve calcification [99]. Additionally, a multicentre family-based cross-sectional study conducted in Switzerland found that elevated plasma levels of dpucMGP were independently and positively correlated with RRI, even after adjusting for various common cardiovascular disease (CVD) risk factors[100] .As previously noted, there is a growing body of evidence suggesting that higher VK intake is linked to improved CVD risk factors, [101,102] and vitamin dependent (VKDP) activity is associated with cardiovascular health through the prevention of vascular calcification [103-105].

Osteopenia and Osteoporosis - Diabetes mellitus (DM) is recognized as a significant risk factor for osteoporotic fractures, with evidence indicating a higher prevalence of osteoporosis among individuals with DM. Vitamin K (VK) is crucial for fracture prevention and the preservation of bone mineral density and overall bone quality [106-109]. In studies involving STZ-induced Type 1 diabetes mellitus (T1DM) rats, a direct relationship was established between hyperglycaemia and a reduction in femoral weight. Notably, administering MK-4 orally five days a week for a duration of 12 weeks effectively mitigated hyperglycaemia and prevented the loss of femoral weight, indicating that VK positively influences cancellous bone mass in STZ-induced T1DM rats [110].

Furthermore, randomized controlled trials examining the link between osteoporosis and VK in postmenopausal women have shown that MK-4 treatment significantly reduces the risk of osteoporotic fractures and lowers serum levels of undercarboxylated osteocalcin (ucOC). However, it remains unclear whether the benefits of MK-4 are associated with an increase in bone mineral density [111-114].

Conclusion

In summary, the connection between Vitamin K and Type 2 Diabetes presents encouraging opportunities for additional research and possible clinical applications. Observational studies indicate a link between sufficient Vitamin K levels and a lower risk of diabetes, while mechanistic investigations clarify Vitamin K's influence on insulin sensitivity and glucose metabolism through mechanisms involving osteocalcin and the modulation of inflammation.

However, there is a need for more rigorous clinical trials to confirm these findings. Current data suggest that Vitamin K, especially K2, may enhance glycaemic control and insulin function, as well as help reduce cardiovascular risk factors commonly associated with Type 2 Diabetes. Consequently, ensuring adequate Vitamin K intake through dietary sources or supplements could be an important aspect of a holistic strategy for managing and potentially preventing Type 2 Diabetes, although further research is essential to validate these conclusions.

Author's contribution-

Concept – Dr Varsha Shirur

Design – Dr Varsha, Dr Aarya,Dr Bhavya

Supervision – Dr Varsha, Dr Deepali Vidhate

Data collection &/or processing – Dr Varsha, Dr Deepali Vidhate,Dr Simran ,Dr Bhavya Vats

Analysis and/or interpretation –Dr Varsha, Dr. Aarya, Dr Bhavya

Literature search – Dr Varsha, Dr Deepali Vidhate, Dr Simran, Dr Bhavya Vats

Writing – Dr Varsha, Dr Deepali Vidhate, Dr Aarya, Dr Bhavya Vats

No conflict of interest

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