

Vitamin K: A Vitamin that Spans Blood, Bones and Carbs

Vitamin K (VitK), a fat-soluble vitamin, is present in the diet in two forms: phyloquinone (K1) and menaquinone (K2). It is found in green leafy vegetables and animal products such as meat, eggs and cheese, respectively. K3 or menadione is a synthetic form of the vitamin. VitK is an essential cofactor required for activation of γ -glutamyl carboxylase, necessary for activation of multiple vitK-dependent proteins (VKDPs). Besides coagulation, VKDPs have roles in bone mineralization, vascular calcification (deficiency associated with risk of arterial and soft-tissue calcification), metabolism (glycaemic control, insulin sensitivity), reproduction, anti-inflammatory properties and cancer progression.^[1]

The current study found vitK2 levels to be significantly lower in type 2 diabetes mellitus (T2DM) patients than in controls. A negative correlation was observed between vitK2, fasting plasma glucose (FPG), 2-h plasma glucose, glycated hemoglobin (HbA1c), fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), total cholesterol and low-density lipoprotein-C (LDL-c). FPG was the only significant independent predictor for serum vitK2 levels.

Epidemiologic studies report a negative association between vitK levels with body mass index (BMI), fat mass, blood glucose, insulin concentrations and insulin resistance. VitK can improve insulin sensitivity by reducing inflammatory cytokines (leptin, tumour necrosis factor (TNF) and interleukin (IL)-6), decreasing total cholesterol and LDL-c and increasing high-density lipoprotein-cholesterol (HDL-c) and adiponectin levels (independent of insulin secretion). Animal studies including both knockout and wild-type mice report the function of osteocalcin in β -cell proliferation, insulin expression and secretion and adiponectin expression in adipocytes. Bone Gla protein (BGP or osteocalcin) is a VKDP along with coagulation factor proteins C, S, M, Z, factors VII, IX, X, prothrombin, matrix Gla protein (MGP), growth arrest-specific 6 protein (Gas6), Gla-rich protein (GRP) and periostin. MGP from vascular smooth muscle cells and chondrocytes inhibits vascular calcification, modulates osteoclastogenesis and affects bone mineralization. BGP or osteocalcin [secreted by osteoblasts and chondrocytes] regulates energy metabolism and male reproductive function through its undercarboxylated form (ucBGP).^[2]

Most clinical studies of vitK on insulin sensitivity and glucose homeostasis have included phyloquinone. In a retrospective analysis of a large Dutch database of vitK intake and incident T2DM over 10 years, it was seen that phyloquinone and menaquinone intakes were inversely associated with the

risk of developing diabetes.^[3] The subsequent 10-year follow-up study of two cohorts (402 women and 400 men, aged 40–80 years) showed that high intakes of menaquinones and high vitK status (and not phyloquinone or total vitK intake) were associated with reduced occurrence of metabolic syndrome (MetS), both cross-sectionally and longitudinally. These associations were mainly driven by triacyl-glycerol and waist circumference.^[4] However, a recent meta-analysis showed that vitK supplementation had no significant effect on fasting blood sugar (FBS), 2-h oral glucose tolerance test (OGTT), HOMA-IR and fasting insulin.^[5]

Interestingly, a recent study from India by Vaidya *et al.*^[6] found that vitamin K2 insufficiency occurred in both the healthy cohort and a cohort of people with diabetes. There seemed to be no difference in this pilot study in the low vitamin K2 levels seen, which was not restricted to individuals with diabetes but was also detected in apparently healthy individuals.

Although the multiple roles of vitK are yet to be ascertained in their entirety, research on VKDPs and vitK-related pathways spanning haematology, bone and diabetes may lead to newer discoveries. Alternatively, vitK levels may be reflective of patients' lifestyle and dietary habits, reflecting a healthier population with a low-calorie diet intake of vegetables and lean meat. It may be akin to vitamin D, where population-based studies consistently show a low prevalence of T2DM and MetS (increased vitamin D levels reflecting more exposure to sunlight, physical activity and a healthier lifestyle), but supplementation has little effect on the incidence of diabetes.

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