Exp Eye Res. 2014 Nov;128:73-82.

# Inhibition of diabetic-cataract by vitamin K1 involves modulation of hyperglycemia-induced alterations to lens calcium homeostasis.

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This study investigated the potential of vitamin K1 against streptozotocin-induced diabetic cataract in Wistar rats. A single, intraperitoneal injection of streptozotocin (STZ) (35 mg/kg) resulted in hyperglycemia, accumulation of sorbitol and formation of advanced glycation end product (AGE) in eye lens. Hyperglycemia in lens also resulted in superoxide anion and hydroxyl radical generation and less reduced glutathione suggesting oxidative stress in lens. Hyperglycemia also resulted in increase in lens Ca2+ and significant inhibition of lens Ca2+ ATPase activity. These changes were associated with cataract formation in diabetic animals. By contrast treatment of diabetic rats with vitamin K1 (5 mg/kg, sc, twice a week) resulted in animals with partially elevated blood glucose and with transparent lenses having normal levels of sorbitol, AGE, Ca2+ ATPase, Ca2+, and oxidative stress. Vitamin K 1 may function to protect against cataract formation in the STZ induced diabetic rat by affecting the homeostasis of blood glucose and minimizing subsequent oxidative and osmotic stress. **Thus, these results show that Vitamin K1 inhibits diabetic-cataract by modulating lens Ca2+ homeostasis and its hypoglycemic effect through its direct action on the pancreas.**

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# Menadione (vitamin K) enhances the antibiotic activity of drugs by cell membrane permeabilization mechanism.

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Menadione, vitamin K3, belongs to the class of lipid-soluble vitamins and lipophilic substances as menadione cause disturbances in the bacterial membrane, resulting in damage to the fundamental elements for the integrity of the membrane, thus allowing increased permeability. Accordingly, the aim of this study was to evaluate in vitro the antibiotic-modifying activity of menadione in multiresistant strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*, with a gradual increase in its subinhibitory concentration. In addition, menadione was compared with cholesterol and ergosterol for similarity in mechanism of drug modulatory action. Antibiotic-modifying activity and antibacterial effect were determined by the broth microdilution assay. **Menadione, cholesterol and ergosterol showed modulatory activity at clinically relevant concentrations, characterizing them as modifiers of bacterial drug resistance, since they lowered the MIC of the antibiotics tested. This is the first report of the antibacterial activity of menadione and its potentiation of aminoglycosides against multiresistant bacteria.**

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# Vitamin K-Dependent Carboxylation of Matrix Gla Protein Influences the Risk of Calciphylaxis.

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**Matrix Gla protein (MGP) is a potent inhibitor of vascular calcification. The** ability of MGP to inhibit calcification requires the activity of a vitamin K-dependent enzyme, which mediates MGP carboxylation. We investigated how MGP carboxylation influences the risk of calciphylaxis in adult patients receiving dialysis and examined the effects of vitamin K deficiency on MGP carboxylation. Our study included 20 patients receiving hemodialysis with calciphylaxis (cases) and 20 patients receiving hemodialysis without calciphylaxis (controls) matched for age, sex, race, and warfarin use. Cases had higher plasma levels of uncarboxylated MGP (ucMGP) and carboxylated MGP (cMGP) than controls. However, the fraction of total MGP that was carboxylated (relative cMGP concentration = cMGP/[cMGP + uncarboxylated MGP]) was lower in cases than in controls (0.58±0.02 versus 0.69±0.03, respectively; P=0.003). In patients not taking warfarin, cases had a similarly lower relative cMGP concentration. Each 0.1 unit reduction in relative cMGP concentration associated with a more than two-fold increase in calciphylaxis risk. Vitamin K deficiency associated with lower relative cMGP concentration in multivariable adjusted analyses (β=-8.99; P=0.04). **In conclusion, vitamin K deficiency-mediated reduction in relative cMGP concentration may have a role in the pathogenesis of calciphylaxis. Whether vitamin K supplementation can prevent and/or treat calciphylaxis requires further study.**

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# Antiparasitic activity of menadione (vitamin K3) against Schistosoma mansoni in BABL/c mice.

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Schistosomiasis is one of the neglected tropical diseases affecting nearly quarter of a billion people in economically challenged tropical and subtropical countries of the world. Praziquantel (PZQ) is the only drug currently available to treat this parasitic disease in spite being ineffective against juvenile worms and concerns about developing resistance to treat reinfections. Our earlier in vitro viability studies demonstrated significant antiparasitic activity of menadione (MEN) (vitamin $K_3$) against Schistosoma mansoni adult worms. To gain insight into plausible mechanism of antischistosomal activity of MEN, its effect on superoxide anion levels in adult worms were studied in vitro which showed significant increases in both female and male worms. Further confirmation of the deleterious morphological changes in their teguments and organelles were obtained by ultrastructural analysis. Genotoxic and cytotoxic studies in

male Swiss mice indicated that MEN was well tolerated at the oral dose of 500mg/kg using the criteria of MNPCE frequency and PCE/RBC ratio in the bone marrow of infected animals. The in vivo antiparasitic activity of MEN was conducted in female BALB/c mice infected with S. mansoni and significant reductions (P<0.001) in total worm burden were observed at single oral doses of 40 and 400mg/kg (48.57 and 61.90%, respectively). Additionally, MEN significantly reduced (P<0.001) the number of eggs in the liver of infected mice by 53.57 and 58.76%, respectively. Similarly, histological analysis of the livers showed a significant reduction (P<0.001) in the diameter of the granulomas. **Since MEN is already in use globally as an over-the-counter drug for a variety of common ailments and a dietary supplement with a safety record in par with similar products when used in recommended doses, the above antiparasitic results which compare reasonably well with PZQ, make a compelling case for considering MEN to treat S. mansoni infection in humans.**

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## Inactive Matrix Gla-Protein and Arterial Stiffness in Type 2 Diabetes Mellitus.

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BACKGROUND: Large artery stiffness is increased in diabetes mellitus and causes an excessive pulsatile load to the heart and to the microvasculature. The identification of pathways related to arterial stiffness may provide novel therapeutic targets to ameliorate arterial stiffness in diabetes. Matrix Gla-Protein (MGP) is an inhibitor of vascular calcification. Activation of MGP is vitamin K dependent. We hypothesized that levels of inactive MGP (dephospho-uncarboxylated MGP; dp-ucMGP) are related to arterial stiffness in type 2 diabetes. METHODS: We enrolled a multiethnic cohort of 66 participants with type 2 diabetes. Carotid-femoral pulse wave velocity (CF-PWV) was measured with high-fidelity arterial tonometry (Sphygmocor Device). Dp-ucMGP was measured with ELISA (VitaK; The Netherlands). RESULTS: The majority of the participants were middle-aged (62 ± 12 years), male (91%), and had a history of hypertension (82%). Average hemoglobin A1C was 7.2% (55 mmol/mol). Mean dp-ucMGP was 624 ± 638 pmol/l and mean CF-PWV was 11 ± 4 m/sec. In multivariable analyses, dp-ucMGP was independently related to African American ethnicity (β = -0.24, P = 0.005), warfarin use (β = 0.56, P < 0.001), and estimated glomerular filtration rate (eGFR, β = -0.32, P < 0.001). Dp-ucMGP predicted CF-PWV (β = 0.40, P = 0.011), even after adjustment for age, gender, ethnicity, mean arterial pressure, eGFR, and warfarin use.

**CONCLUSIONS: In our cross-sectional analysis, circulating dp-ucMGP was independently associated with CF-PWV in type 2 diabetes. This suggests that deficient vitamin K-dependent activation of MGP may lead to large artery stiffening and could be targeted with vitamin K supplementation in the patients with diabetes.**