

SELECTED ABSTRACTS

CALGENEX

NATURAL INGREDIENTS TO ADDRESS SOFT TISSUE CALCIFICATION

Vitamin K in the Treatment and Prevention of Osteoporosis and Arterial Calcification

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Am J Health-Syst Pharm. 2005;62(15):1574-1581.

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Purpose: The role of vitamin K in the prevention and treatment of osteoporosis and arterial calcification is examined. **Summary:** Vitamin K is essential for the activation of vitamin K-dependent proteins, which are involved not only in blood coagulation but in bone metabolism and the inhibition of arterial calcification. In humans, vitamin K is primarily a cofactor in the enzymatic reaction that converts glutamate residues into γ -carboxyglutamate residues in vitamin K-dependent proteins. Numerous studies have demonstrated the importance of vitamin K in bone health. The results of recent studies have suggested that concurrent use of menaquinone and vitamin D may substantially reduce bone loss. Menaquinone was also found to have a synergistic effect when administered with hormone therapy. Several epidemiologic and intervention studies have found that vitamin K deficiency causes reductions in bone mineral density and increases the risk of fractures. Arterial calcification is an active, cell-controlled process that shares many similarities with bone metabolism. Concurrent arterial calcification and osteoporosis have been called the "calcification paradox" and occur frequently in postmenopausal women. The results of two dose-response studies have indicated that the amount of vitamin K needed for optimal γ -carboxylation of osteocalcin is significantly higher than what is provided through diet alone and that current dosage recommendations should be increased to optimize bone mineralization. Few adverse effects have been reported from oral vitamin K. **Conclusion:** Phytonadione and menaquinone may be effective for the prevention and treatment of osteoporosis and arterial calcification.

Dietary Intake of Menaquinone Is Associated with a Reduced Risk of Coronary Heart Disease: The Rotterdam Study

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ABSTRACT Vitamin K-dependent proteins, including matrix Gla-protein, have been shown to inhibit vascular calcification. Activation of these proteins via carboxylation depends on the availability of vitamin K. We examined whether dietary intake of phylloquinone (vitamin K-1) and menaquinone (vitamin K-2) were related to aortic calcification and coronary heart disease (CHD) in the population-based Rotterdam Study. The analysis included 4807 subjects with dietary data and no history of myocardial infarction at baseline (1990–1993) who were followed until January 1, 2000. The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone compared to the lower tertile [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (0.75, 1.09) and 0.74 (0.59, 0.92), respectively] and severe aortic calcification [odds ratio of 0.71 (0.50, 1.00) and 0.48 (0.32, 0.71), respectively]. Phylloquinone intake was not related to any of the outcomes. These findings suggest that an adequate intake of menaquinone could be important for CHD prevention.

Inhibitors of calcification in blood and urine.

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Semin Dial. 2007 Mar-Apr;20(2):113-21

In bone and teeth formation, coordinated calcification is a highly desirable biological process. However, heterotopic calcification at unwanted tissue sites leads to dysfunction, disease and, potentially, to death and therefore requires prevention and treatment. With the recent discovery of calcification inhibitors we now know that biological calcification is not passive but a complex, active and highly regulated process. Calcification at vascular sites is the most threatening localization and manifests as part of atherosclerosis or arteriosclerosis. Atherosclerosis is often accompanied by intimal plaque calcification, whereas arteriosclerosis is characterized by calcification of the media. The severity of calcification of cerebral or coronary atherosclerotic plaques is associated with an increased incidence of events such as stroke or myocardial infarction. Medial calcification is the major cause of arterial stiffness, which contributes to left ventricular dysfunction and heart failure. Patients with chronic kidney disease are at especially increased risk for both intimal and medial calcification. In this context, it is currently thought that calcium-regulatory factors including fetuin-A, matrix Gla protein, osteoprotegerin, and pyrophosphates act in a local or systemic manner to prevent calcifications of the vasculature, and that dys-regulations of such calcification inhibitors may contribute to progressive calcifications. Nephrolithiasis represents another process of unwanted calcification responsible for significant morbidity. More than 80% of renal stones contain calcium. Urinary factors inhibiting calcification are citrate, glycosaminoglycans, Tamm-Horsfall protein, and osteopontin. This review summarizes current experimental and clinical data underlining the biological importance of these calcification inhibitors.

Vitamin D Deficiency and Risk of Cardiovascular Disease.

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Circulation. 117(4):503-511, January 29, 2008.

Background-: Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle, endothelium, and cardiomyocytes. A growing body of evidence suggests that vitamin D deficiency may adversely affect the cardiovascular system, but data from longitudinal studies are lacking.

Methods and Results-: We studied 1739 Framingham Offspring Study participants (mean age 59 years; 55% women; all white) without prior cardiovascular disease. Vitamin D status was assessed by measuring 25-dihydroxyvitamin D (25-OH D) levels. Prespecified thresholds were used to characterize varying degrees of 25-OH D deficiency (<15 ng/mL, <10 ng/mL). Multivariable Cox regression models were adjusted for conventional risk factors. Overall, 28% of individuals had levels <15 ng/mL, and 9% had levels <10 ng/mL. During a mean follow-up of 5.4 years, 120 individuals developed a first cardiovascular event. Individuals with 25-OH D <15 ng/mL had a multivariable-adjusted hazard ratio of 1.62 (95% confidence interval 1.11 to 2.36, P=0.01) for incident cardiovascular events compared with those with 25-OH D ≥15 ng/mL. This effect was evident in participants with hypertension (hazard ratio 2.13, 95% confidence interval 1.30 to 3.48) but not in those without hypertension (hazard ratio 1.04, 95% confidence interval 0.55 to 1.96). There was a graded increase in cardiovascular risk across categories of 25-OH D, with multivariable-adjusted hazard ratios of 1.53 (95% confidence interval 1.00 to 2.36) for levels 10 to <15 ng/mL and 1.80 (95% confidence interval 1.05 to 3.08) for levels <10 ng/mL (P for linear trend=0.01). Further adjustment for C-reactive protein, physical activity, or vitamin use did not affect the findings.

Conclusions-: Vitamin D deficiency is associated with incident cardiovascular disease. Further clinical and experimental studies may be warranted to determine whether correction of vitamin D deficiency could contribute to the prevention of cardiovascular disease.

Taurine inhibits osteoblastic differentiation of vascular smooth muscle cells via the ERK pathway.

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Amino Acids. 2007 Dec 4

Vascular calcification develops within atherosclerotic lesions and results from a process similar to osteogenesis. Taurine is a free beta-amino acid and plays an important physiological role in mammals. We have recently demonstrated that vascular smooth muscle cells (VSMCs) express a functional taurine transporter. To evaluate the possible role of taurine in vascular calcification, we assessed its effects on osteoblastic differentiation of VSMCs *in vitro*. The results showed that taurine inhibited the beta-glycerophosphate-induced osteoblastic differentiation of VSMCs as evidenced by both the decreasing alkaline phosphatase (ALP) activity and expression of the core binding factor alpha1 (Cbfa1). Taurine also activated the extracellular signal-regulated protein kinase (ERK) pathway. Inhibition of ERK pathway reversed the effect of taurine on ALP activity and Cbfa1 expression. These results suggested that taurine inhibited osteoblastic differentiation of vascular cells via the ERK pathway.

Magnesium therapy for nephrolithiasis.

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Magnes Res. 2005 Jun;18(2):123-6.

PURPOSE:Critically evaluate the experimental evidence and clinical trial outcomes as the basis for use of magnesium (Mg) supplements as therapy for calcium oxalate nephrolithiasis. **MATERIALS AND METHODS:** Literature search of MedLine and Web of Science through January 2005; articles cited in papers found by searches. **RESULTS:** Magnesium inhibits calcium oxalate crystallization in human urine and model systems. Magnesium also inhibits absorption of dietary oxalate from the gut lumen. Three early trials of Mg oxide (MgO) and Mg hydroxide (Mg(OH)₂) reported lower rates of recurrent stone formation. However in a double-blind, randomized, placebo-controlled trial with more carefully selected patients, there was no significant difference between recurrence rates with 650 or 1300 mg MgO daily and the placebo. Another trial reported 391 mg (21 meq) Mg daily as a mixed salt, Mg potassium citrate, reduced calcium stone recurrence by 90%, similar to potassium citrate, but with better gastrointestinal tolerance. The failure of MgO and Mg(OH)₂ as sole therapy may be related to poor absorption and low rates of Mg deficiency in the patient populations tested. **CONCLUSIONS:** Clinical trial evidence does not justify the use of MgO or Mg(OH)₂ as a sole therapy for calcium oxalate kidney stones in a general patient population. However, the addition of magnesium to potassium citrate therapy improves outcomes. Clinical trials should focus on patients who are likely to be Mg deficient.

Relation of ascorbic acid to coronary artery calcium: the Coronary Artery Risk Development in Young Adults Study.

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Am J Epidemiol. 2004 Mar 15;159(6):581-8.

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Ascorbic acid is an antioxidant nutrient possibly related to the development of atherosclerosis. To examine the relation between ascorbic acid and coronary artery calcium, an indicator of subclinical coronary disease, the authors analyzed data from 2,637 African-American and White men and women aged 18-30 years at baseline who were enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study (1985-2001). Participants completed diet histories at enrollment and year 7, and plasma ascorbic acid levels were obtained at year 10. Coronary artery computed tomography was performed at year 15. The authors calculated odds ratios in four biologically relevant plasma ascorbic acid categories, adjusting for possible confounding variables. When compared with men with high plasma ascorbic acid levels, men with low levels to marginally low levels had an increased prevalence of coronary artery calcium (multivariate odds ratio = 2.68, 95% confidence interval: 1.31, 5.48). Among women, the association was attenuated and nonsignificant (multivariate odds ratio = 1.50, 95% confidence interval: 0.58, 3.85). Ascorbic acid intakes from diet alone and diet plus supplements were not associated with coronary artery calcium. Low to marginally low plasma ascorbic acid levels were associated with a higher prevalence of coronary artery calcium among men but not among women.

Regulatory role of vitamins E and C on extracellular matrix components of the vascular system.

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Mol Aspects Med. 2007 Oct-Dec;28(5-6):507-37.

The protective effect of vitamins E (alpha-tocopherol) and C (L-ascorbic acid) in the prevention of cardiovascular disease (CVD) has been shown in a number of situations but a secure correlation is not universally accepted. Under certain conditions, both, L-ascorbic acid and alpha-tocopherol can exhibit antioxidant properties and thus may reduce the formation of oxidized small molecules, proteins and lipids, which are a possible cause of cellular de-regulation. However, non-antioxidant effects have also been suggested to play a role in the prevention of atherosclerosis. Vitamin E and C can modulate signal transduction and gene expression and thus affect many cellular reactions such as the proliferation of smooth muscle cells, the expression of cell adhesion and extracellular matrix molecules, the production of O₂(-) by NADPH-oxidase, the aggregation of platelets and the inflammatory response. Vitamins E and C may modulate the extracellular matrix environment by affecting VSMC differentiation and the expression of connective tissue proteins involved in vascular remodeling as well as the maintenance of vascular wall integrity. This review summarizes individually the molecular activities of vitamins E and C on the cells within the connective tissue of the vasculature, which are centrally involved in the maintenance of an intact vascular wall as well as in the repair of atherosclerotic lesions during disease development.

Calcification in coronary artery disease can be reversed by EDTA-tetracycline long-term chemotherapy.

Maniscalco BS, Taylor KA.

Pathophysiology. 2004 Oct;11(2):95-101.

Atherosclerosis is a complex process with multiple mechanisms and factors contributing to its initiation and progression. Detection and quantification of coronary artery calcium (CAC) scores with electron beam tomography has been shown to correlate with obstructive and nonobstructive coronary artery disease (CAD). Pathogen-triggered calcification could play a role in CAD. Recent reports suggest that infectious blood nanobacteria (NB) emerge to be such a trigger. So far, minimal or no reversal of atherosclerosis has been claimed by therapies with iv ethylenediaminetetraacetic acid disodium salt (EDTA), antibiotics, or other regimens, and therapies for atherosclerosis remain non-curative. We have now combined EDTA with antibiotic tetracycline (comET), an in vitro proven nanobacteriocidal treatment, and tested comET therapy in patients with documented CAD. Three hypotheses were probed: (1) Are NB present in patients with CAD?; (2) Does treatment with comET affect blood NB antigen and serology?; (3) Does a comET decrease CAC scores? One hundred patients with stable CAD and positive CAC scores were enrolled into a 4 month study of comET therapy. ComET therapy is composed of (1) Nutraceutical Powder (Vitamin C, Vitamin B6, Niacin, Folic Acid, Selenium, EDTA, l-Arginine, l-Lysine, l-Ornithine, Bromelain, Trypsin, CoQ10, Grapeseed Extract, Hawthorn Berry, Papain) 5cm(3) taken orally every evening; (2) Tetracycline HCl 500mg taken orally every evening; (3) EDTA 1500mg taken in a rectal suppository base every evening. CAC scoring was repeated at 4 months and serum samples were analyzed for NB antigen and serology at baseline, 2 and 4 months. Complete blood count, metabolic panel, liver function, C-reactive protein (hs-CRP) and lipids were analyzed at baseline and 4 months. Seventy-seven patients completed the study and all patients were positive for NB serology, antigen or both. Responders (n = 44; 57%) had significant decreases in total CAC scores (P = 0.001), the average decrease being 14%. Non-responders (n = 33; 44%) had no change or had increases in CAC scores. Angina was decreased or ablated in 16 of 19 patients (84%). Lipid profiles improved to non-atherogenic direction significantly (P = 0.001), a remarkable finding in a patient group where 86% were on continuous statin medication already before the trial. No adverse physiologic effects were seen in renal, hepatic, or hematopoietic systems. In conclusion, CAC scores decreased during ComET therapy trial in most CAD patients inferring regression of calcified coronary artery plaque volume. The patients tolerated the therapy well and their angina and lipid profiles improved. Further treatment trials for long term therapy with matched controls are warranted.