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ABSTRACTS

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Vitamin K and Bone mass in Women

Vitamin K status and bone mass in women with and without aortic atherosclerosis: a population-based study

Calcif Tissue Int 1996 Nov;59(5):352-6

Gammacarboxyglutamate (Gla) is an uncommon amino acid formed by vitamin K action. Increasing evidence indicates that Gla-proteins are involved in the regulation of calcification processes in both bone tissue and atherosclerotic vessel wall. In a population-based study we have previously shown that in a group of 113 postmenopausal women the presence of abdominal aortic calcifications is associated with a reduced vitamin K status. In the present study we investigated whether this reduced vitamin K status was also associated with differences in bone mass or circulating calciotropic hormone levels. Serum immunoreactive osteocalcin with low affinity for hydroxyapatite (irOCfree) was used as a marker for vitamin K status. After correction for age it was found that women with atherosclerotic calcifications had a 7% lower bone mass as measured by metacarpal radiogrammetry (mean difference: 3.2 mm², 95% CI: -0.2-6.5, P = 0.06). No differences between both groups of women were observed for serum intact parathyroid hormone (PTH) and serum 25-hydroxyvitamin D levels. In the atherosclerotic women (n = 34), markers for vitamin K status were inversely associated with bone mass (r = -0.47, P = 0.013), whereas no such association was found in the nonatherosclerotic women (n = 79). It is concluded that the atherosclerotic women in this study may be at higher risk for osteoporotic fractures as evidenced by their lower bone mass and higher serum irOCfree levels. The finding that in atherosclerotic women vitamin K status is associated with bone mass supports our hypothesis that vitamin K status affects the mineralization processes in both bone and in atherosclerotic plaques.

Vitamin K and the Nervous System

Vitamin K-dependent proteins in the developing and aging nervous system

Nutr Rev 1999 Aug;57(8):231-40

Although the warfarin embryopathy syndrome, with its neurologic and bone abnormalities, has been known for decades, the role of vitamin K in the brain has not been studied systematically. Recently, it was demonstrated that vitamin K-dependent carboxylase expression is temporally regulated in a tissue-specific manner with high expression in the nervous system during the early embryonic stages and with liver expression after birth and in adult animals. This finding, along with the discovery of wide distribution of the novel vitamin K-dependent growth factor, Gas6, in the central nervous system, provides compelling evidence of a biologic role of vitamin K during the development of the nervous system. In animals and bacteria, vitamin K was observed to influence the brain sulfatide concentration and the activity and synthesis of an important enzyme involved in brain sphingolipids biosynthesis. Taken together, previous research results point to a possible role of vitamin K in the nervous system, especially during its development. Hence, the knowledge of the biologic role of vitamin K in the brain may be important for unveiling the mechanisms of normal and pathologic development and aging of the nervous system. The role of the vitamin K-dependent protein Gas6 in activation of signal transduction events in the brain in light of the age-related changes in the nervous system is also discussed.

Vitamin K use for Treatment of Tumors

Apoptosis provoked by the oxidative stress inducer menadione (Vitamin K(3)) is mediated by the Fas/Fas ligand system

Clin Immunol 1999 Oct;93(1):65-74

Menadione, or vitamin K(3) (VK(3)), a potent oxidative stress inducer, has been recently used as an effective and remarkably safe cytotoxic drug for treatment of several human tumors. VK(3) induces apoptotic cell death through a poorly understood mechanism. Here we show for the first time that VK(3)-induced apoptosis requires the Fas/FasL system. Spleen cells from both Fas- and FasL-deficient mice (C57BL/6-lpr and C57BL/6-gld, respectively) had much lower levels of VK(3) apoptosis in vitro compared to cells from control C57BL/6 mice. VK(3) cytotoxicity toward mouse splenocytes was also blocked with a Fas-Fc fusion protein. VK(3) induced apoptosis in Jurkat cells, coincident with an increase in both Fas and FasL expression. A FasL-resistant variant of these Jurkat cells was also resistant to VK(3)-induced apoptosis. Furthermore, because VK(3) effects were inhibited by glutathione, a potent antioxidant, oxidative stress was linked to the Fas/FasL system. Moreover, since the Jurkat cell lines were p53 null, the activation of Fas/FasL system after oxidative stress apparently acted through a p53-independent pathway. The therapeutic relevance of the K vitamins has been growing in recent years; our findings offer new insight for improving and expanding their applications.

Aspirin and Anticoagulants Compared

A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicentre unblinded randomised clinical trial

BMJ 1996 Dec 7;313(7070):1429-31

OBJECTIVE: To compare aspirin with anticoagulation with regard to risk of cardiac death and reinfarction in patients who received anistreplase thrombolysis for myocardial infarction. **DESIGN:** A multicentre unblinded randomised clinical trial. **SETTING:** 38 hospitals in six countries. **SUBJECTS:** 1036 patients who had been treated with anistreplase for myocardial infarction were randomly assigned to either aspirin (150 mg daily) or anticoagulation (intravenous heparin followed by warfarin or other oral anticoagulant). The trial was stopped earlier than originally intended because of the slowing rate of recruitment. **MAIN OUTCOME MEASURE:** Cardiac death or recurrent myocardial infarction at 30 days. **RESULTS:** After 30 days cardiac death or reinfarction, occurred in 11.0% (57/517) of the patients treated with anticoagulation and 11.2% (58/519) of the patients treated with aspirin (odds ratio 1.02, 95% confidence interval 0.69 to 1.50, $P = 0.92$). Corresponding findings at three months were 13.2% (68/517) and 12.1% (63/519) (0.91, 0.63 to 1.32, $P = 0.67$). Patients receiving anticoagulation were more likely than patients receiving aspirin to have had severe bleeding or a stroke by three months (3.9% v 1.7% (0.44, 0.20 to 0.97, $P = 0.04$)). **CONCLUSION:** No evidence of a difference in the incidence of cardiac events was found between the two treatment groups, though the trial is too small to claim treatment equivalence confidently. A higher incidence of severe bleeding events and strokes was detected in the group receiving anticoagulation, suggesting that aspirin may be the drug of choice for most patients in this context.

Aspirin's Effect on Cytokines

Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin

Circulation 1999 Aug 24;100(8):793-8

BACKGROUND: Proinflammatory cytokines released by injured endothelium facilitate interaction of endothelial cells with circulating leukocytes and thus may contribute to development and progression of atherosclerosis. We investigated whether cytokines and C-reactive protein (CRP) are indicative of myocardial ischemia or of diseased vessels and whether they are influenced by aspirin treatment in patients with chronic stable angina. **METHODS AND RESULTS:** Plasma macrophage colony stimulating factor (MCSF), IL-1b, IL-6, and CRP were measured in 60 stable patients after 48-hour Holter monitoring and in 24 matched controls. All patients had angiographic documentation of disease and positive exercise ECGs. Patients with ischemia on Holter monitoring (n=40) received aspirin or placebo in a 6-week, randomized, double blind, crossover trial. Blood sampling was repeated at the end of each treatment phase (3 weeks). Compared to controls, patients had more than twice median MCSF (800 versus 372 pg/mL), IL-6 (3.9 versus 1.7 pg/mL), and CRP (1.25 versus 0.23 mg/L) levels ($P<0.01$ for all comparisons). MCSF was related to ischemia on Holter monitoring ($P<0.01$), to low ischemic threshold during exercise ($P<0.01$), and together with IL-1b to number of diseased vessels ($P<0.05$). MCSF, IL-6, and CRP were all reduced after 6 weeks of aspirin treatment ($P<0.05$). **CONCLUSIONS:** These findings suggest that cytokines are associated with both ischemia and anatomic extent of disease in patients with stable angina. Reduced cytokine and CRP levels by aspirin may explain part of aspirin's therapeutic action.

Aspirin and Cardiovascular Disease

Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men

N Engl J Med 1997 Apr 3;336(14):973-9

BACKGROUND: Inflammation may be important in the pathogenesis of atherothrombosis. We studied whether inflammation increases the risk of a first thrombotic event and whether treatment with aspirin decreases the risk. **METHODS:** We measured plasma C-reactive protein, a marker for systemic inflammation, in 543 apparently healthy men participating in the Physicians' Health Study in whom myocardial infarction, stroke, or venous thrombosis subsequently developed, and in 543 study participants who did not report vascular disease during a follow-up period exceeding eight years. Subjects were randomly assigned to receive aspirin or placebo at the beginning of the trial. **RESULTS:** Base-line plasma C-reactive protein concentrations were higher among men who went on to have myocardial infarction (1.51 vs. 1.13 mg per liter, $P<0.001$) or ischemic stroke (1.38 vs. 1.13 mg per liter, $P=0.02$), but not venous thrombosis (1.26 vs. 1.13 mg per liter, $P=0.34$), than among men without vascular events. The men in the quartile with the highest levels of C-reactive protein values had three times the risk of myocardial infarction (relative risk, 2.9; $P<0.001$) and two times the risk of ischemic stroke (relative risk, 1.9; $P=0.02$) of the men in the lowest quartile. Risks were stable over long periods, were not modified by smoking, and were independent of other lipid-related and non-lipid-related risk factors. The use of aspirin was associated with significant reductions in the risk of myocardial infarction (55.7 percent reduction, $P=0.02$) among men in the highest quartile but with only small, nonsignificant reductions among those in the lowest quartile (13.9 percent, $P=0.77$). **CONCLUSIONS:** The base-line plasma concentration of C-reactive protein predicts the risk of future myocardial infarction and stroke. Moreover, the reduction associated with the use of aspirin in the risk of a first myocardial infarction appears to be directly related to the level of C-reactive protein, raising the possibility that antiinflammatory agents may have clinical benefits in preventing cardiovascular disease.

CLA and Prostate Cancer

Opposite effects of linoleic acid and conjugated linoleic acid on human prostatic cancer in SCID mice

Anticancer Res 1998 May-Jun;18(3A):1429-34

The relationship between dietary fat intake (level and type) and cancer development is a matter of concern in Western society. The purpose of this study was to determine the effect of three different diets on the local growth and metastatic properties of DU-145 human prostatic carcinoma cells in severe combined immunodeficient (SCID) mice. Animals were fed a standard diet or diets supplemented with 1% LA or 1% CLA for 2 weeks prior to subcutaneous (s.c.) inoculation of DU-145 cells and throughout the study (total of 14 weeks). Mice receiving LA-supplemented diet displayed significantly higher body weight, lower food intake and increased local tumor load as compared to the other two groups of mice. Mice fed the CLA-supplemented diet displayed not only smaller local tumors than the regular diet-fed group, but also a drastic reduction in lung metastases. These results support the view that dietary polyunsaturated fatty acids may influence the prognosis of prostatic cancer patients, thus opening the possibility of new therapeutic options.

Conjugated linoleic acid and linoleic acid are distinctive modulators of mammary carcinogenesis

Nutr Cancer 1997;27(2):131-5

Previous work by Ip and co-workers showed that mammary cancer prevention by conjugated linoleic acid (CLA) is independent of the level of fat in the diet. Because CLA is an isomer of linoleic acid, there is the question regarding whether the effect of CLA is due to a displacement of linoleic acid in cells. To further evaluate whether there might be an interaction between linoleic acid and CLA, the present study was designed to examine the dose response to CLA (at 0.5%, 1%, 1.5%, and 2%) in rats fed a 2% or a 12% linoleate diet (both basal diets contained 20% total fat by weight). The end points of investigation included the bioassay of mammary tumorigenesis in the rat dimethylbenz[a]anthracene model as well as the incorporation of CLA, linoleic acid, and arachidonic acid in mammary glands. The mammary carcinogenesis results showed that the efficacy of tumor suppression by CLA was not affected by linoleate intake. With either linoleate diet, no further protection was evident with levels of CLA > 1%. Analysis of neutral lipids and phospholipids of the mammary tissue indicated that 1) the accumulation of CLA in mammary tissue was dose dependent from 0.5% to 2%, 2) CLA concentration was 10 times higher in neutral lipids than in phospholipids, 3) the incorporation of CLA in either fraction was not affected by the availability of linoleic acid, and 4) CLA did not appear to displace linoleic acid or arachidonic acid in the mammary tissue. The above findings suggest that there may be distinctive mechanisms in the modulation of tumor development by linoleic acid and CLA.

Dietary CLA's Increase Lean Fat

Dietary conjugated linoleic acids increase lean tissue and decrease fat deposition in growing pigs

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Conjugated linoleic acids (CLA) decrease the body fat content of rodents; the aim of this study was to determine whether dietary CLA altered carcass composition of pigs. Female Large White x Landrace pigs (n = 66) were used in this study. To obtain initial body composition, six pigs were slaughtered at 57 kg live weight, whereas the remaining pigs were allocated to one of six dietary treatments (0, 1.25, 2.5, 5.0, 7.5 and 10.0 g/kg CLA, containing 55% of CLA isomers). The diets, containing 14.3 MJ digestible energy (DE) and 9.3 g available lysine per kg, were fed ad libitum for 8 wk. Dietary CLA had no significant effect on average daily gain (861 vs. 911 g/d for pigs fed diets with and without CLA, P = 0.15) or feed intake (2.83 vs. 2.80 kg/d, P = 0.74). The gain to feed ratio was increased by dietary CLA by 6.3% (0.328 vs. 0.348, P = 0.009). Fat deposition decreased linearly (-8.2 +/- 2.09 g/d for each gram per kilogram increase in CLA concentration; P < 0.001) with increasing inclusion of CLA. At the highest level of CLA inclusion, fat deposition was decreased by 88 g/d (-31%). Similarly, the ratio of fat to lean tissue deposition decreased linearly (-0.093 +/- 0.0216 for each gram per kilogram increase in CLA concentration; P < 0.001) with increasing dietary CLA. The carcass lean tissue deposition response to dietary CLA was quadratic in nature and was maximized (+25%) at 5.0 g/kg dietary CLA. Overall, dietary CLA increased the gain to feed ratio and lean tissue deposition and decreased fat deposition in finisher pigs.

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