

LE Magazine April 2003

ABSTRACTS

Silicon

Effects of germanium and silicon on bone mineralization.

The chemical properties of germanium (Ge) are similar to silicon (Si). This study investigated whether Ge can substitute for, or is antagonistic to, Si in bone formation. Sixty male weanling Sprague-Dawley rats were randomly assigned to treatment groups of 12 and 6 in a 2 x 4 factorially arranged experiment. The independent variables were, per gram fresh diet, Si (as sodium metasilicate) at 0 or 25 micrograms and Ge (as sodium germanate) at 0, 5, 30 or 60 micrograms. Results confirmed that Ge does not enhance Si deprivation and provided evidence that Ge apparently can replace Si in functions that influence bone composition. When Si was lacking in the diet, calcium and magnesium concentrations of the femur were decreased; this was reversed by feeding either Ge and/or Si. Similar effects were found for zinc, sodium, iron, manganese and potassium of vertebra. There were some responses to Si deprivation that Ge could not reverse; Ge did not increase femur copper, sodium or phosphorus or decrease molybdenum of vertebra, effects that were evoked by Si supplementation. Additionally, some findings suggested that 60 micrograms Ge/g diet could be a toxic intake for the rat. On the other hand, some responses induced by Ge indicate that this element may be acting physiologically other than as a substitute for Si. Germanium itself affected bone composition. Germanium supplementation decreased Si and molybdenum in the femur and increased DNA in tibia. Regardless of the amount of Si fed, animals fed 30 micrograms Ge/g diet had increased tibial DNA compared to animals fed 0 or 60 micrograms Ge; however, tibial DNA of animals fed 30 micrograms Ge was not statistically different from those animals fed 5 micrograms Ge. Thus, Ge may be of nutritional importance.

Biol Trace Elem Res 1994 Aug;42(2):151-64

Silicon deprivation decreases collagen formation in wounds and bone, and ornithine transaminase enzyme activity in liver.

We have shown that silicon (Si) deprivation decreases the collagen concentration in bone of nine-week-old rats. Finding that Si deprivation also affects collagen at different stages in bone development, collagen-forming enzymes or collagen deposition in other tissues would have implications that Si is important for both wound healing and bone formation. Therefore, 42 rats in experiment one and 24 rats in experiment two were fed a basal diet containing 2 or 2.6 microg Si/g, respectively, based on ground corn and casein, and supplemented with either 0 or 10 microg Si/g as sodium metasilicate. At three weeks, the femur was removed from 18 of the 42 rats in experiment one for hydroxyproline analysis. A polyvinyl sponge was implanted beneath the skin of the upper back of each of the 24 remaining rats. Sixteen hours before termination and two weeks after the sponge had been implanted, each rat was given an oral dose of 14C-proline (1.8 microCi/100 g body wt). The total amount of hydroxyproline was significantly lower in the tibia and sponges taken from Si-deficient animals than Si-supplemented rats. The disintegrations per minute of 14C-proline were significantly higher in sponge extracts from Si-deficient rats than Si-supplemented rats. Additional evidence of aberrations in proline metabolism with Si deprivation was that liver ornithine aminotransferase was significantly decreased in Si-deprived animals in experiment two. Findings of an increased accumulation of 14C-proline and decreased total hydroxyproline in implanted sponges and decreased activity of a key enzyme in proline synthesis (liver ornithine aminotransferase) in Si-deprived animals indicates an aberration in the formation of collagen from proline in sites other than bone that is corrected by Si. This suggests that Si is a nutrient of concern in wound healing as well as bone formation.

Biol Trace Elem Res 2002 Dec;89(3):251-61

Stem cells

Eradication of multiple myeloma and breast cancer cells by TH9402-mediated photodynamic therapy: implication for clinical ex vivo purging of autologous stem cell transplants.

High-dose chemotherapy combined with autologous transplantation using bone marrow or peripheral blood-derived stem cells (PBSC) is now widely used in the treatment of hematologic malignancies as well as some solid tumors like breast cancer (BC). However, some controversial results were recently obtained in the latter case. The presence of malignant cells in the autograft has been associated with the recurrence of the disease, and purging procedures are needed to eliminate this risk. The aim of this study was to evaluate the potential of the photosensitizer 4,5-dibromorhodamine methyl ester (TH9402), a dibrominated rhodamine

derivative, to eradicate multiple myeloma (MM) and BC cell lines, while sparing more than 50% of normal pluripotential blood stem cells from healthy volunteers. The human BC MCF-7 and T-47D and MM RPMI 8226 and NCI-H929 cell lines were used to optimize the photodynamic purging process. Cell concentration and the cell suspension thickness as well as the dye and light doses were varied in order to eventually treat 1-2 L of apheresis. The light source consisted of two fluorescent scanning tubes emitting green light centered about 515 nm. The cellular uptake of TH9402 was measured during the incubation and washout periods and after photodynamic treatment (PDT) using spectrofluorometric analysis. The limiting dilution assay showed that an eradication rate of more than five logs is obtained when using a 40 minute incubation with 5 to 10 microM dye followed by a 90 minute washout period and a light dose of 5 to 10 J/cm² (2.8 mW/cm²) in all cell lines. Agitating the 2 cm thick cell suspension containing 20 x 10⁶ cells/mL during PDT was essential for maximal photoinactivation. Experiments on mobilized PBSC obtained from healthy volunteers showed that even more drastic purging conditions than those found optimal for maximal eradication of the malignant cell lines were compatible with a good recovery of hematopoietic progenitors cells. The absence of significant toxicity towards normal hematopoietic stem cells, combined with the five logs eradication of cancer cell lines induced by this procedure suggests that TH9402 offers an excellent potential as an ex vivo photodynamic purging agent for autologous transplantation in MM and BC treatment.

Photochem Photobiol 2000 Dec;72(6):780-7

Prevention of graft-versus-host disease while preserving graft-versus-leukemia effect after selective depletion of host-reactive T cells by photodynamic cell purging process.

In this study, we investigated the possibility of selective depletion of donor alloantigen-specific T-cells from C57BL/6 (H-2(b)) mice to prevent graft-versus-host disease (GVHD). These cells were first activated with irradiated BALB/c (H-2(d)) host spleen cells in a five-day mixed lymphocyte culture. Following this activation, a photoactive rhodamine derivative called 4,5-dibromorhodamine 123 (TH9402), was added. This compound is selectively retained in the mitochondria of activated host-reactive cells but not tumor- or third-party-specific resting cells. The treated cells were subsequently exposed to visible light (514 nm) to deplete the TH9402-enriched activated host-reactive cells. Treatment with photodynamic cell purging process (PDP) inhibited antihost responses measured by cytotoxic T-lymphocytes (CTL) by 93%, and interferon-gamma production by 66%. By contrast, anti-BCL1 (BALB/c-origin leukemia/lymphoma) and anti-third-party C3H/HeJ (H-2(k)) responses were preserved. PDP-treated primed C57BL/6 cells were further tested in vivo. All lethally irradiated BALB/c mice inoculated with BCL1 cells and T-cell-depleted bone marrow cells developed leukemia by day +30, with 50% mortality by 100 days. All mice died of GVHD after addition of 5 x 10⁶ untreated primed C57BL/6 cells. However, addition of same numbers of PDP-treated cells allowed 90% of the recipients to survive more than 100 days without detectable BCL1 tumor cells and free of GVHD. Moreover, PDP-treated primed C57BL/6 cells retained the ability to induce GVHD in the third-party C3H/HeJ mice. These data suggest that PDP can selectively deplete host alloantigen-specific T-cells for GVHD prevention and immune and antileukemia function preserve.

Blood 2002 May 1;99(9):3083-8

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ABSTRACTS

Coenzyme Q10

Neuronal death in the rat hippocampus in experimental diabetes and cerebral ischaemia treated with antioxidants.

Male Wistar rats were subjected to intraperitoneal (i.p.) streptozotocin (STZ) administration (85 mg/kg) to evoke diabetes. Cerebral ischaemia was produced by injection of 0.03 ml of air into the left carotid followed by bilateral common carotid ligation. We studied the effect of application of two antioxidants-coenzyme Q10 (CoQ10, 10 mg/kg b.w., i.p. for seven days) and lipoic acid (LA, 100 mg/kg b.w., i.p. for seven days) on neurones and on the apoptosis-related enzyme-caspase-3 activity in the hippocampus and dentate gyrus. Ischaemia and diabetes lead to a decrease of nuclear and perikaryon diameters as well as neuronal density in the CA1, CA2, CA3 and dentate gyrus. Application of CoQ10 or LA for seven days improved the mean nucleus area and perikaryon area in almost all investigated structures. Both antioxidants diminished neuronal loss in the diabetes complicated with ischaemia but not in the animals with diabetes only. Activity of one of the key enzymes in apoptotic cell death, caspase-3 (CPP32), increased in hippocampus in the diabetic rats, in the animals with cerebral ischaemia and in the rats with both diabetes and ischaemia by about 80%, 33% and 53%, respectively. Either the CoQ10 or the LA treatment led to a significant decrease of the CPP32 activity in all experimental groups. Our results confirm the presence of neuronal damage and death in the hippocampus and dentate gyrus in the experimental STZ-diabetes and its aggravation by the additional cerebral ischaemia. The effects of the antioxidative treatment support the hypothesis of an important role of oxidative stress and free radicals in neuronal pathology in diabetes and ischaemia. The above results of CPP32 activity suggest an important role of apoptosis as a mechanism of cell death and demonstrate the positive effect of the CoQ10 and the LA treatment.

Folia Neuropathol 2001;39(3):147-54

Ubiquinone (coenzyme q10) and mitochondria in oxidative stress of Parkinson's disease.

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease affecting approximately 1% of the population older than 50 years. There is a worldwide increase in disease prevalence due to the increasing age of human populations. A definitive neuropathological diagnosis of Parkinson's disease requires loss of dopaminergic neurons in the substantia nigra and related brain stem nuclei, and the presence of Lewy bodies in remaining nerve cells. The contribution of genetic factors to the pathogenesis of Parkinson's disease is increasingly being recognized. A point mutation which is sufficient to cause a rare autosomal dominant form of the disorder has been recently identified in the alpha-synuclein gene on chromosome 4 in the much more common sporadic, or 'idiopathic' form of Parkinson's disease, and a defect of complex I of the mitochondrial respiratory chain was confirmed at the biochemical level. Disease specificity of this defect has been demonstrated for the parkinsonian substantia nigra. These findings and the observation that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which causes a Parkinson-like syndrome in humans, acts via inhibition of complex I have triggered research interest in the mitochondrial genetics of Parkinson's disease. Oxidative phosphorylation consists of five protein-lipid enzyme complexes located in the mitochondrial inner membrane that contain flavins (FMN, FAD), quinoid compounds (coenzyme Q10, CoQ10) and transition metal compounds (iron-sulfur clusters, hemes, protein-bound copper). These enzymes are designated complex I (NADH:ubiquinone oxidoreductase, EC 1.6.5.3), complex II (succinate:ubiquinone oxidoreductase, EC 1.3.5.1), complex III (ubiquinol:ferrocytochrome c oxidoreductase, EC 1.10.2.2), complex IV (ferrocytochrome c: oxygen oxidoreductase or cytochrome c oxidase, EC 1.9.3.1), and complex V (ATP synthase, EC 3.6.1.34). A defect in mitochondrial oxidative phosphorylation, in terms of a reduction in the activity of NADH CoQ reductase (complex I) has been reported in the striatum of patients with Parkinson's disease. The reduction in the activity of complex I is found in the substantia nigra, but not in other areas of the brain, such as globus pallidus or cerebral cortex. Therefore, the specificity of mitochondrial impairment may play a role in the degeneration of nigrostriatal dopaminergic neurons. This view is supported by the fact that MPTP generating 1-methyl-4-phenylpyridine (MPP(+)) destroys dopaminergic neurons in the substantia nigra. Although the serum levels of CoQ10 is normal in patients with Parkinson's disease, CoQ10 is able to attenuate the MPTP-induced loss of striatal dopaminergic neurons.

Biol Signals Recept 2001 May-Aug;10(3-4):224-53

Vitamin D

A cost-effectiveness analysis of calcium and vitamin D supplementation, etidronate and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids.

OBJECTIVE: To assess the relative costs and benefits of calcium and vitamin D supplements, cyclic etidronate or alendronate in the prevention of vertebral fractures for women with normal bone density and osteopenia who are about to initiate moderate dose

glucocorticoid treatment. METHODS: Using a decision analysis model, we evaluated the following patients: four hypothetical cohorts: 30-yr-old women with normal lumbar spine (LS) bone mineral density (BMD) (t score = 0), 50-yr-old women with borderline osteopenia (t score = -1), 60-yr-old women with moderate osteopenia (t score = -1.5) and 70-yr-old women with severe osteopenia (t score = -2) treated with a mean prednisone dose of 10 mg/day for one year. The main outcomes included the development of vertebral fractures 10-years after glucocorticoid treatment and at age 80 (life-time risk) and direct and indirect costs. RESULTS: At 10 years, calcium and vitamin D supplements decreased fracture rates by 30% to 50% at a minimal cost (US\$800 or less per vertebral fracture avoided) or at a cost saving compared to no treatment for women with osteopenia (t score -1 to -2). Etidronate and alendronate are most cost-effective in women with borderline osteoporosis (t scores of -1.5 and -2) in the 10 year analysis. In the lifetime analysis, calcium and vitamin D treatment yielded a cost savings compared to no treatment for all groups with osteopenia. Etidronate decreased fracture rates further in all groups at a cost of less than \$2,000 per fracture prevented. Alendronate reduced the fracture risk further at cost of \$3,000 to \$7,000 per fracture avoided. CONCLUSION: Calcium and vitamin D supplements and low cost bisphosphonate regimens such as cyclic etidronate decrease the lifetime vertebral fracture risk at acceptable costs and should be considered when initiating glucocorticoid treatment for women who do not have osteoporosis.

J Rheumatol 2003 Jan;30(1):132-8

A rationale for vitamin D prescribing in a falls clinic population.

OBJECTIVE: To assess the prevalence of vitamin D insufficiency in a falls clinic population. To identify simple clinical predictors of vitamin D insufficiency. DESIGN: Prospective observational descriptive study. PARTICIPANTS: 400 consecutive patients who attended a falls clinic taking referrals from a casualty department or general practitioners. RESULTS: Hypovitaminosis D is very common, affecting at least 72% of a falls clinic population. The number of times an individual goes out per week and serum albumin are independent predictors of hypovitaminosis D, but the predictive value is low. CONCLUSIONS: The prevalence of vitamin D insufficiency is high in a falls clinic population. It is difficult to predict which individuals are most at risk within this population. The benefits of vitamin D supplementation in older people are well recognized. Therefore in the absence of toxic effects, a pragmatic approach may be to supplement all attendees at a falls clinic.

Age Ageing 2002 Jul;31(4):267-71

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