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Vitamin D: more than a bone regulator

Editorial

Vitamin D is best known for the bone manifestation called rickets that occurs in children with a vitamin D deficiency. Rickets was first recognised as a public health problem at the time of the industrial revolution, when many people lived in highly polluted towns with little sunlight. The main function of vitamin D, however, is to maintain blood levels of calcium and phosphorus at the levels needed for vital processes such as muscle contraction, nervous transmission,

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blood clotting and cell membrane integrity, as well as bone mineralization. Numerous enzyme systems involved in protein, lipid and energy metabolism also depend on a constant supply of calcium and phosphorus that is made available through the actions of vitamin D.

Strictly speaking, vitamin D is not a vitamin at all, but a “prohormone” that is produced in the skin by solar radiation. This is first metabolised in the liver, then converted to its biologically most active form (calcitriol) in the kidneys. So, with adequate sunlight exposure, we should not need to obtain vitamin D from our food at all. Unfortunately, most people who live in Europe north of latitude 40° (i.e. north of Madrid, Rome, Istanbul) have insufficient sunlight exposure in winter, and so synthesize little or no vitamin D in the skin for three to six months of the year. Dark-skinned people, elderly and women who cover themselves when outdoors are also likely to produce less vitamin D than they need even in the summer months. So, for many Europeans, a dietary source of vitamin D is essential. However, the only foods that naturally provide substantial amounts are fatty fish and fish-liver oils, while eggs, milk and dairy products have moderate amounts. Meat, vegetables, fruits and nuts have little or no vitamin D at all. Margarine fortified with vitamin D can be bought in a few countries in Europe.

This means that many Europeans must be in a quasi-permanent suboptimal state with respect to vitamin D. While this might not be severe enough to cause soft bones (osteomalacia) or muscle weakness, it could influence health in other ways. Research has shown, for example, that vitamin D is important for other vital functions not related to calcium and phosphorus homeostasis (biological equilibrium), and recent hypotheses suggest that a vitamin D deficiency increases the risk of developing cancer (especially breast, prostate and colon cancer), tuberculosis, cardiovascular disorders, diabetes, schizophrenia, depression and autoimmune disorders such as multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease [Zittermann — For other recent papers, see PRISM 2004/2 pages 6+7; PRISM 2005/1 page 3; this issue pages 3+4].

If these theories are confirmed, it will become even more important to ensure an optimal vitamin D status. The oral dose needed to achieve this is probably much higher than the current recommendation of 200–600 IU (5–15 µg) daily.

A. Bowley

References

Zittermann A. *Vitamin D in preventive medicine: are we ignoring the evidence?* *Brit J Nutr* 2003; 89: 552–572.

NUTRITION AND BONE HEALTH

Early identification of bone fracture risk important**Review**

After the menopause, at least one woman in three is affected by osteoporosis. Osteoporotic bone fractures are therefore a serious health problem in the western world. Early identification of women at risk can be achieved by screening bone mineral density.

Bone loss can be slowed by achieving an adequate status of calcium and vitamin D. For many individuals, this requires regular intake of a supplement. Weight-bearing exercise also improves muscle strength/coordination and helps to prevent falls. Hormone replacement is usually considered as one of the most effective ways to prevent postmenopausal osteoporosis and is recommended by experts as the first option. Medical treatment to reduce bone loss (e.g. bisphosphonates) is also widely used. A new generation of potential bone-building drugs derived from human parathyroid hormone is emerging, but its use is currently restricted because of uncertainties related to the risk involved.

Conclusion

It is important that women with low bone density are identified early, and that adequate measures are taken to slow bone loss and reduce the risk of osteoporotic fractures. These include supplementation with calcium and vitamin D.

Source

Kaplan B, Hirsch M. Current approach to fracture prevention in postmenopausal osteoporosis. Clin Exp Obstet Gyn 2004; 4: 251–255.

To reduce bone fracture risk elderly people need more vitamin D**Review**

Bone fractures caused by osteoporosis are a growing concern for health authorities. Their high prevalence and treatment costs, as well as the loss in quality of life for those affected, call for an effective, low-cost and well-tolerated prevention strategy. One possibility is to give a vitamin D supplement. To determine the efficacy of such supplementation, Bischoff-Ferrari et al. reviewed the available published evidence.

The analysis of five randomised controlled trials for hip fracture and seven for nonvertebral fracture involving a total of more than 19'100 persons over sixty years of age showed that a daily dose of 700–800 IU vitamin D is needed to reduce the risk of hip fracture by 26% and the risk of nonvertebral fracture by 23%. A daily dose of 400 IU vitamin D had no significant effect on fracture risk.

Conclusion

A daily dose of 400 IU (10 µg) vitamin D is not enough to reduce the risk of hip and other nonvertebral fractures in the elderly; at least 700 IU (17.5 µg) daily are needed.

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Source

Bischoff-Ferrari HA, Willett, WC, Wong JB, et al. Fracture prevention with vitamin D supplementation; a meta-analysis of randomized controlled trials. J Amer Med Ass 2005; 293: 2257–2264.

Postmenopausal women on weight-loss diet need more calcium**Intervention**

Obese postmenopausal women on a weight-reduction diet are susceptible to increased bone loss, which can be prevented with calcium supplementation. To investigate the influence of energy restriction and calcium intake on bone mineral density of overweight postmenopausal women, Riedt et al. subjected 47 such women to a six-month weight-reduction diet providing either 1 g or 1.7 g calcium daily (partly as a supplement). As controls they included 19 overweight women who did not lose weight, and whose diet (including a supplement) provided 1 g calcium daily.

With normal calcium intake (1 g daily) women who lost weight lost more bone mineral in the trochanter (end of the femur) and spine than those with a high calcium intake or women with normal calcium intake who did not lose weight.

Conclusion

To minimise bone loss during a weight-reduction diet, overweight postmenopausal women need a daily calcium intake of at least 1.7 g.

Source

Riedt CS, Cifuentes M, Stahl T, et al. Overweight postmenopausal women lose bone with moderate weight reduction and 1 g/day calcium intake. J Bone Miner Res 2005; 20: 455–463.

NUTRITION IN PREGNANCY AND LACTATION

Vitamin D supplements should be given routinely in pregnancy**Review**

The risk of developing multiple sclerosis, a chronic disease of the nervous system that disables those affected, increases with increasing distance from the Equator. This has been attributed to the lower exposure of individuals to sunlight and their subsequent suboptimal vitamin D status. Studies have shown a protective effect of sunlight and vitamin D supplementation. Chaudhuri discusses the possible mechanisms and weighs the evidence supporting the routine use of vitamin D during pregnancy.

The cause of multiple sclerosis is unknown, and there is no effective treatment available. Children conceived in autumn or winter appear to have a higher risk of developing the disorder. Although little is known about the role of vitamin D in the central nervous system, studies have shown that the biologically active form of vitamin D can modulate the production of growth factors,

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neurotransmitters and neurotrophins (molecules that encourage survival of nerve cells) in the brain. Vitamin D could therefore be required for the survival and differentiation of oligodendroglia, the cells that form the protective coating around nerves, which is impaired in multiple sclerosis.

Conclusion

The assumption that vitamin D nutrition is adequate in the absence of rickets is probably flawed, and existing recommendations are probably too low. All adults, and especially pregnant/lactating women should take a supplement containing 1000 IU (25 µg) vitamin D daily.

Source

Chaudhuri A. Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis. Med Hypotheses 2005; 64: 608–618.

Prolonging folic acid supplementation might prevent late pregnancy complications

Survey

To assess if folic acid supplementation in late pregnancy is potentially beneficial for maternal health, Holmes et al. measured homocysteine and folate status in 101 pregnant women at 12, 20 and 35 weeks of gestation, and in 35 nonpregnant controls (sampled concurrently). They also took samples from 21 mothers three days after delivery, together with 19 nonpregnant controls.

Homocysteine levels were consistently lower during pregnancy (especially in those 90% who took folic acid during the first trimester) than in controls. Values were lowest in the second trimester and increased towards nonpregnant levels in the third trimester. By the third day after delivery, levels were similar in both groups. Women with a history of miscarriage had significantly higher levels in the third trimester than women with no such history.

Conclusion

Continuing folic acid supplementation beyond (the currently recommended) twelve weeks of pregnancy may help to prevent late complications associated with high blood homocysteine levels, such as preeclampsia.


Source

Holmes VA, Wallace JMW, Alexander HD, et al. Homocysteine is lower in the third trimester of pregnancy in women with enhanced folate status from continued folic acid supplementation. Clin Chem 2005; 51: 629–634.

Value of supplementation to prevent birth defects confirmed

Survey

To confirm the validity of the results from the 1984–1991 Hungarian randomised controlled trial of periconceptual multivitamin supplementation, Czeizel et al. recruited women from the Hungarian Periconceptual Service

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who were using the same supplement as in the earlier study and compared pregnancy outcomes with unsupplemented women matched for age, socioeconomic status, etc.

In each of the two cohorts, they evaluated 3056 offspring. They registered 51 congenital abnormalities in the supplemented group (1 neural tube defect, 31 cardiovascular defects, 14 urinary tract defects including 2 cases of stenosis at the pelvoureteric junction, 1 limb defect and 4 orofacial clefts) and 86 in the control group (9 neural tube defects, 50 cardiovascular defects, 19 urinary tract defects including 13 cases of stenosis at the pelvoureteric junction, 3 limb defects, 3 orofacial clefts and 2 cases of pyloric stenosis).

Conclusion

This second Hungarian intervention trial confirms the efficacy of multivitamin supplementation (containing 0.8 mg folic acid) in the prevention of neural tube defects, congenital abnormalities of the cardiovascular system and obstructive congenital abnormalities of the urinary tract. Such supplementation therefore has significant medical benefit.

Source

Czeizel AE, Dobó M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital malformations. Birth defects Res 2004; 70: 853–861.

PREVENTION OF CANCER

Antioxidants lower cancer risk in female smokers

Intervention

To measure the cancer-preventive effect of antioxidant supplementation in smokers, Mooney et al. assessed DNA damage in 96 men and 80 women before, during and after 15 months' treatment with an antioxidant supplement (500 mg vitamin C and 400 IU vitamin E daily) or a placebo. At baseline, all participants smoked ≥ 10 cigarettes daily, and had a serum cotinine (main metabolite of nicotine) level ≥ 25 ng/ml. Blood samples were analysed every three months for benzo(a)pyrene-DNA adducts (a marker of lung cancer risk in smokers).

Among women who took the supplement for 15 months, benzo(a)pyrene-DNA adducts decreased by 31%; in treated women with the protective gene GSTM1, adducts decreased by 43%. No effect was found in men.

Conclusion

Benzo(a)pyrene-DNA adducts were significantly reduced in women smokers on antioxidant supplementation (but not in men). Nevertheless, the best way to reduce cancer risk is to stop smoking.

Source

Mooney LA, Madsen AM, Tang D, et al. Antioxidant vitamin supplementation reduces benzo(a)pyrene-DNA adducts and potential cancer risk in female smokers. Cancer Epidemiol Biomarkers Prev 2005; 14: 237–241.

PREVENTION OF CARDIOVASCULAR DISEASE

Folic acid reduces lipid peroxidation in uraemic patients

Review

Cardiovascular disease is the main cause of death in patients with kidney disease requiring dialysis. Recent hypotheses add high blood homocysteine, inflammation and oxidative stress to the factors involved in the development of atherosclerosis in these patients. Bayés et al. discuss the roles of these factors and the evidence for their validity.

Statistical analysis found no correlation between the three factors. Markers of inflammation and lipid peroxidation reliably predict mortality risk, but homocysteine levels in patients on folic acid do not. The authors' own research has shown that intravenous administration of folinic acid (an active form of folic acid) lowers homocysteine levels subordinate to patients' inflammatory status, and implies that supplementation has an antioxidant effect.

Conclusion

Findings confirm that inflammation and oxidative stress, together with age, are the main predictors of mortality risk in patients with chronic kidney disease. The reduction in lipid peroxidation after folic acid supplementation shows why it is important to understand these "new" risk factors to prevent development of atherosclerosis in such patients.

Source

*Bayés B, Pastor MC, Bonal J, Romero R. "New" cardiovascular risk factors in patients with chronic kidney disease: role of folic acid treatment. *Kidney Internat* 2005; 65: S39–S43.*

NUTRITION AND MENTAL HEALTH

Integrated treatment improves cognitive function in dementia

Intervention

To evaluate the efficacy of an integrated treatment on long-term cognitive function, Bragin et al. measured a battery of psychological tests in 35 elderly patients diagnosed with mild dementia and depression before starting treatment, and after 6, 12 and 24 months on antidepressants, cholinesterase inhibitors (drugs against Alzheimer's disease) and multivitamin/antioxidant supplements. The patients were also provided with diet recommendations, and learned how to manage stress and relax, and how to exercise physically.

Treatment was well tolerated. Tests for attention, reaction time, memory, word fluency and cognition improved consistently over the whole treatment period. Depressive symptoms were resolved within six months.

Conclusion

The observed results suggest that integrated treatment (with specific medications, antioxidants, vitamins, diet and exercise) of patients with mild

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to moderate dementia and depression could bring improvements in cognitive function that persist for up to two years.

Source

Bragin V, Chemodanova M, Dzhafarova N, et al. Integrated treatment approach improves cognitive function in demented and clinically depressed patients. Am J Alzheimers Dis Other Demen 2005; 20: 21–26.

Vitamin E might delay development of Alzheimer's disease

Review

Although the brain accounts for less than 2% of total body weight, it uses up to a quarter of available body oxygen. High levels of unsaturated lipids in the brain are susceptible to oxidative damage, and this is considered an important event in the development of neurodegenerative disorders such as Alzheimer's disease. Low brain levels of vitamin E are common in patients with Alzheimer's disease, suggesting that supplementation with vitamin E might have a protective effect. Recent placebo-controlled studies in patients with moderate Alzheimer's disease seem to confirm this. The reason why vitamin E behaves as an antioxidant in the cerebrospinal fluid, but as a prooxidant in the blood is related to major differences in oxidative conditions in the two body fluids.

Conclusion

Vitamin E appears to prevent oxidation of lipids in the brain and cerebrospinal fluid, and could offer new perspectives in the treatment of Alzheimer's disease.

Source

Kontush A, Schekatolina S. Vitamin E in neurodegenerative disorders: Alzheimer's disease. Ann NY Acad Sci 2004; 1031: 249–262.

THERAPEUTIC APPLICATIONS

High doses of oral B12 can correct deficiency in elderly

Intervention

Vitamin B12 deficiency often occurs in old age as a result of poor absorption, and should be suspected in individuals with unspecific tiredness or malaise. It is usually treated with intramuscular injections of 1000 µg vitamin B12 at monthly intervals. To estimate how much oral vitamin B12 is needed to correct deficiency, Eussen et al. enrolled 120 healthy men and women over 70 years of age who met the criteria for mild vitamin B12 deficiency (low serum B12 and high methylmalonic acid levels) to a sixteen-week course of vitamin B12 supplementation. Participants were randomised to daily doses of 2.5, 100, 250, 500 or 1000 µg cyanocobalamin.

The authors calculated that 647–1032 µg cyanocobalamin daily was the lowest oral dose able to achieve 80–90% of the estimated maximum reduction in plasma methylmalonic acid.

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Conclusion

In elderly people with mild vitamin B12 deficiency, a daily oral dose of at least 600 µg cyanocobalamin (200 times the recommended dietary allowance) is needed to normalize blood levels of methylmalonic acid (a biochemical marker of deficiency) and vitamin B12 status.

Source

Eussen SJPM, de Groot LCPGM, Clarke R, et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency. A dose-finding trial. Arch Intern Med 2005; 165: 1167–1172.

GENERAL NUTRITION

More efforts needed to improve girls' and women's diet quality**Review**

Dietary quality is important for women's health, not only during childbearing years, pregnancy and lactation, but also during childhood and old age. A poor micronutrient status not only impairs a woman's own health, but can also affect the health of the next generation. Worldwide, most women still do not obtain adequate amounts of vitamins and minerals from their food. An approach is therefore required that considers nutrition holistically, and does not simply focus on single nutrients.

Conclusion

New paradigms for micronutrient interventions that can result in significant health improvement, better pregnancy and infant outcomes, and economic benefits worldwide should emphasize prevention more than cure, promote healthy lifestyles, and ensure micronutrient adequacy to women and girls throughout the life cycle. Women should be encouraged to take supplements when their needs are not met by dietary or food fortification approaches.

Source

Bartley KA, Underwood BA, Deckelbaum RJ. A life cycle micronutrient perspective for women's health. Am J Clin Nutr 2005; 81: 1188S–1193S.

Supplement use by young Germans declining**Survey**

To identify patterns and time trends in supplement use by healthy children and adolescents between 1986 and 2003, Sichert-Hellert and Kersting examined 5'990 three-day records from 931 participants aged 2–18 years in the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study.

Supplement usage was mentioned in almost 26% of the records (13.2% males, 12.6% females). Users were more likely to come from families of non-smokers, where the mothers were better educated and employed outside of

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the home. Fluorine was the most commonly consumed supplement (18.1% – mostly by children under 4 years), followed by vitamins (4.5%), vitamin/mineral combinations (3.6%) and minerals (2.4%). Multiple usage was reported by 2.6%. The nutrients most frequently used were vitamin C (72%), thiamine (57%) riboflavin (54%), calcium (44%), magnesium (31%) and phosphorus (20%). Supplement usage increased from 1986 to reach a peak in 1994/96. Since then it has declined steadily.

Conclusion

Use of supplements by German children and adolescents is common and changing with time. Type of supplement and frequency of use are age dependent. The nutrients found in most supplements are not the critical ones.

Source

Sichert-Hellert W, Kersting M. Vitamin and mineral supplements use in German children and adolescents between 1986 and 2003: results of the DONALD study. Ann Nutr Metab 2004; 48: 414–419.