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VitaMind™

Practitioner Information

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Table of Contents

OVERVIEW 1
- Dosage and Safety 13
- Modern Medical View of Nutrients 13
- Vitamins-as-Prevention 13
- Vitamins-as-Treatment 14
- Vitamins are Non-Toxic 14
- Health Canada Views Vitamins as Preventing Deficiency Disease 15
- Comparing Deaths Due To Nutrients And Deaths Due To Drugs 15
- The Precautionary Principle 15
- Doctors Do Not Learn About Nutrition 15
- Introducing the Strauss Questionnaires 16

EVALUATION QUESTIONNAIRES 17
- Strauss Mood Questionnaire 17
- The Strauss Social Readjustment Rating Scale (SSRRS) 18

VITAMIN A (RETINYL PALMITATE) 21
- Vitamin A Deficiency 21
- Vitamin A Toxicity 22
- Vitamin A References 23

VITAMIN C (ASCORBIC ACID) 26
- Vitamin C Deficiency 26
- Vitamin C References 28

VITAMIN D (CHOLECALCIFEROL) 31
- Vitamin D Deficiency and Dependency 31
- Vitamin D Toxicity 34
- Vitamin D References 35

VITAMIN E (D-ALPHA TOCOPHERYL SUCCINATE) 36
- Vitamin E Deficiency 36
- Vitamin E Toxicity 38
- Vitamin E References 38

VITAMIN B1 (THIAMINE MONONITRATE) 42
- Thiamine Deficiency and Dependency 42
- Vitamin B1 References 45

VITAMIN B2 (RIBOFLAVIN) 48
- Riboflavin Deficiency 48
- Vitamin B2 References 49

VITAMIN B3 (NIACINAMIDE) 52
- Niacin Deficiency 52
- Vitamin B3 References 54

VITAMIN B5 (D-CALCIUM PANTOTHENATE) 59
Pantothenic Acid Deficiency 59
Vitamin B5 References 60

VITAMIN B6 (PYRIDOXINE HYDROCHLORIDE) 62
Vitamin B6 Deficiency and Dependency 62
Vitamin B6 Toxicity 63
Vitamin B6 References 63

VITAMIN B9 (FOLIC ACID) 65
Folic Acid Deficiency 65
Folic Acid Excess 66
Vitamin B9 References 66

VITAMIN B12 70
Vitamin B12 Deficiency 70
Vitamin B12 References 71

VITAMIN H (BIOTIN) 75
Biotin Deficiency and Dependency 75
Biotin References 75

CALCIUM 79
Hypocalcemia 79
Hypercalcemia 80
Calcium References 81

PHOSPHORUS 84
Phosphate Metabolism 84
Phosphorus References 85

MAGNESIUM 86
Magnesium Metabolism 86
Disorders of Magnesium Metabolism 86
Hypomagnesemia 86
Drug Interactions Merck 88
Hypermagnesemia 88
Magnesium References 88

POTASSIUM 93
Hypokalemia 93
Hyperkalemia 94
Potassium References 95

IODINE (FROM PACIFIC KELP) 96
Iodine Deficiency 96
Iodine References 97

ZINC 101
- Zinc Deficiency 101
- Zinc Excess 102
- Zinc References 102

SELENIUM 105
- Selenium Deficiency 105
- Selenium Excess 106
- Selenium References 106

COPPER 110
- Copper Deficiency 110
- Copper Excess 111
- Copper References 111

MANGANESE 115
- Manganese References 115

CHROMIUM 117
- Chromium Picolinate 117
- Chromium References 118

MOLYBDENUM 119
- Molybdenum References 119

IRON 122
- Iron Deficiency 122
- Iron Excess 124
- Iron References 124

CITRUS BIOFLAVANOIDS 128
- Citrus Bioflavanoids References 128

GRAPE SEED EXTRACT 129
- Grape Seed Extract References 129

CHOLINE 130
- Choline References 130

INOSITOL 131
- Inositol References 131

GINKGO BILOBA 132
- Ginkgo Biloba References 132

METHIONINE 134
- L-Methionine 134
- Methionine References 135

VANADIUM 137
Vanadium References 137
BORON 138
Boron References 138
APPENDIX A: RDA AND UL LIMITS 139
APPENDIX B: CENTER FOR SCIENCE IN THE PUBLIC INTEREST: NOV. 10, 2003 140
Food Companies Undermine Parents, Overfeed Kids 140
APPENDIX C 142
Text References 142

OVERVIEW

Strauss Herb Co., working in collaboration with experts in the manufacture of other significant multi-nutrient products, has developed the Strauss VitaMind™ formula. VitaMind™ is a broad spectrum multi-vitamin/mineral/herbal blend designed to support cognitive function and emotional stability in the general population.

At Strauss, we believe VitaMind™ is a nutritional supplement that will assist and support normal mental functions and mood stability in normal, healthy people when they are under physical or mental stress from a multitude of possible causes, including diet, alcohol, medications, environment, workplace, relationships, and aging.

1. Gonzalez-Gross M, Marcos A, Pietrzik K. Nutrition and cognitive impairment in the elderly. Br J Nutr. 2001 Sep;86(3):313-21. "Research in this area has been intensive during the last decade, and results indicate that subclinical deficiency in essential nutrients (antioxidants such as vitamins C, E and beta-carotene, vitamin B(12), vitamin B(6), folate) and nutrition-related disorders, as hypercholesterolaemia, hypertriacylglycerolaemia, hypertension, and diabetes could be some of the nutrition-related risk factors, which can be present for a long time before cognitive impairment becomes evident.."

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As the number of older people is growing rapidly worldwide and the fact that elderly people are also apparently living longer, dementia, the most common cause of cognitive impairment is getting to be a greater public health problem. Nutrition plays a role in the ageing process, but there is still a lack of knowledge about nutrition-related risk factors in cognitive impairment. Research in this area has been intensive during the last decade, and results indicate that subclinical deficiency in essential nutrients (antioxidants such as vitamins C, E and beta-carotene, vitamin B(12), vitamin B(6), folate) and nutrition-related disorders, as hypercholesterolaemia, hypertriacylglycerolaemia, hypertension, and diabetes could be some of the nutrition-related risk factors, which can be present for a long time before cognitive impairment becomes evident. Large-scale clinical trials in high-risk populations are needed to determine whether lowering blood homocysteine levels reduces the risk of cognitive impairment and may delay the clinical onset of dementia and perhaps of Alzheimer's disease. A curative treatment of cognitive impairment, especially Alzheimer's disease, is currently impossible. Actual drug therapy, if started early enough, may slow down the progression of the disease. Longitudinal studies are required in order to establish the possible link of nutrient intake--nutritional status with cognitive impairment, and if it is possible, in fact, to inhibit or delay the onset of dementia..

Publication Types:
* Review
* Review, Academic

PMID: 11570983 [PubMed - indexed for MEDLINE]

2. Dror Y, Stern F, Berner YN, Kaufmann NA, Berry E, Maaravi Y, Altman H, Cohen A, Leventhal A, Kaluski DN. Micronutrient (vitamins and minerals)

supplementation for the elderly, suggested by a special committee nominated by Ministry of Health. Harefuah. 2001 Nov;140(11):1062-7, 1117.

Institute of Biochemistry Food Science and Nutrition, Faculty of Agriculture, Hebrew University, Israel.

The elderly tend to be at a higher risk for nutritional deficiencies and in particular for micronutrient deficiencies. A committee nominated by Ministry of Health examined the relevant literature and the local recommendations as well as the recommendations from other countries and suggested a daily special micronutrient supplementation for institutionalized elderly. The preparatory will contain about half the RDA for most of the micronutrients, except for fluorine that is recommended at a lower level and biotin, vitamins D, C, B12 as well as zinc, copper and molybdenum at a level higher than half the RDA. Major elements such as calcium, are not included in the preparatory and would be supplied separately when needed. Vitamin K and iron are excluded as well. The suggested preparatory composition, mg: vitamin A, 0.450; vitamin D, 0.015; vitamin E, 10; thiamin, 0.6 Pound riboflavin, 0.7; biotin, 0.030; pantothenic acid, 3; niacin, 8; vitamin C, 60; vitamin B6, 0.8; folic acid, 0.120; vitamin B12, 0.0024; choline up to 275; zinc, 8; copper, 0.9; fluorine, 0.5; manganese, 1.2; chromium 0.020; molybdenum, 0.045; selenium, 0.030; and iodine, 0.075. Fat-soluble vitamins should be microencapsulated. Micronutrient supplementation is part of Ministry of Health balanced nutrition policy. The committees recommendations are also applicable for the free-living elderly.

Publication Types:
* Review
* Review Literature

PMID: 11759383 [PubMed - indexed for MEDLINE]

3. Keen CL, Clegg MS, Hanna LA, Lanoue L, Rogers JM, Daston GP, Oteiza P, Uriu-Adams JY. The plausibility of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications. J Nutr. 2003 May;133(5 Suppl 2):1597S-1605S.

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Numerous studies support the concept that a major cause of pregnancy complications can be suboptimal embryonic and fetal nutrition. Although the negative effects of diets low in energy on pregnancy outcome are well documented, less clear are the effects of diets that are low in one or more essential micronutrients. However, several observational and intervention studies suggest that diets low in essential vitamins and minerals can pose a significant reproductive risk in diverse human populations. Although maternal nutritional deficiencies typically occur as a result of low dietary intakes of essential nutrients, nutritional deficiencies at the level of the conceptus can arise through multiple mechanisms. Evidence from experimental animals supports the concept that in addition to primary deficiencies, secondary embryonic and fetal nutritional deficiencies can be caused by diverse factors including genetics, maternal disease, toxicant insults and physiological stressors that can trigger a maternal acute phase response. These secondary responses may be significant contributors to the occurrence of birth defects. An implication of the above is that the frequency and severity of pregnancy

complications may be reduced through an improvement in the micronutrient status of the mother.

Publication Types:
* Review
* Review, Academic

PMID: 12730474 [PubMed - indexed for MEDLINE]

4. Turner-McGrievy GM, Barnard ND, Scialli AR, Lanou AJ. Effects of a low-fat vegan diet and a Step II diet on macro- and micronutrient intakes in overweight postmenopausal women. Nutrition. 2004 Sep;20(9):738-46.

Physicians Committee for Responsible MedicineWashington, DC, USA.

OBJECTIVE: This study investigated the nutrient intake of overweight postmenopausal women assigned to a low-fat vegan diet or a Step II diet. METHODS: Fifty-nine overweight (body mass index, 26 to 44 kg/m(2)) postmenopausal women were randomly assigned to a self-selected low-fat vegan or a National Cholesterol Education Program Step II diet in a 14-wk controlled trial on weight loss and metabolism. Nutrient intake, which was measured per 1000 kcal, was the main outcome measure. Statistical analyses included within-group and between-group t tests examining changes associated with each diet. RESULTS: Consumption of a low-fat vegan diet was associated with greater decreases in fat, saturated fat, protein, and cholesterol intakes and greater increases in carbohydrate, fiber, beta-carotene, and total vitamin A intakes than was a Step II diet. The low-fat vegan group also increased thiamin, vitamin B6, and magnesium intakes more than the Step II group, and both groups increased folic acid, vitamin C, and potassium intakes. If considering only food sources of micronutrients, the low-fat vegan group decreased vitamin D, vitamin B12, calcium, selenium, phosphorous, and zinc intakes compared with baseline. However, with incidental supplements included, decreases were evident only in phosphorous and selenium intakes. No micronutrient decreases were found in the Step II group. CONCLUSIONS: Individuals on a low-fat vegan or Step II diet should take steps to meet the recommended intakes of vitamin D, vitamin K, folic acid, calcium, magnesium, and zinc. Individuals on a low-fat vegan diet should also ensure adequate intakes of vitamin B12, phosphorous, and selenium..

PMID: 15325679 [PubMed - in process]

5. Black MM. Micronutrient deficiencies and cognitive functioning. J Nutr. 2003 Nov;133(11 Suppl 2):3927S-3931S.

Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD 21201, USA. mblack@umaryland.edu

The relationship between four micronutrient deficiencies (iodine, iron, zinc and vitamin B-12) and children's cognitive functioning is reviewed. Iodine deficiency during pregnancy has negative and irreversible effects on the developing fetus. Although there is some evidence that postnatal iodine deficiency is associated with cognitive deficits, the findings are controversial. Iron deficiency is widespread and has been associated to cognitive deficits, but the results of prevention trials are inconsistent. Zinc deficiency has been linked with low activity and depressed motor development among the most vulnerable children. Associations with cognitive

development are less clear and may be limited to specific neuropsychological processes. Vitamin B-12 deficiency has been associated with cognitive problems among the elderly, but little is known about its effect on children's cognitive functioning. Rates of vitamin B-12 deficiency are likely to be high because animal products are the only source of vitamin B-12. Although micronutrient deficiencies often co-occur in the context of poverty, little is known about the impact of multiple micronutrient deficiencies on cognitive development..

Publication Types:
* Review
* Review, Tutorial

PMID: 14672291 [PubMed - indexed for MEDLINE]

6. Bienz D, Cori H, Hornig D. Adequate dosing of micronutrients for different age groups in the life cycle. Food Nutr Bull. 2003 Sep;24(3 Suppl):S7-15.

Micronutrient Intervention Project, Roche Vitamins Ltd., CH-4070 Basel, Switzerland. denise.bienz@roche.com

Many studies of micronutrient supplementation in developing countries have used single-nutrient supplements with either vitamins or minerals. However, people in these countries often suffer from multiple, rather than single, micronutrient deficiencies. The objective of this paper is to discuss the factors that go into determining the adequate dosing of vitamins and/or minerals for people of different ages. To elaborate on the adequacy of micronutrient doses in supplements, a model described by the US FNB was used, which calculates the difference between the mean observed intake for an individual and the estimated average requirement for a life stage and gender group. This model allows estimating the degree of confidence that a certain nutrient intake (from supplements and diet) is adequate. The US/Canadian DRI values have been used as the basis for these calculations, from which it can be concluded that a daily supplement of one RDA of each micronutrient is adequate to cover the personal requirements of all individuals in each respective age and gender group of the population, provided that 20 to 40% of an RDA is supplied by the diet--likely a realistic value for developing countries. DRI values vary significantly between different age groups, reflecting changing needs over a life cycle. With the objective of a supplement to be adequate and safe, the design of a one-for-all supplement covering all age groups is not realistic. Such a supplement would either underscore or surpass the required intake of some of the age groups. Additionally the dosage of certain micronutrients might exceed the upper level of intake for lower age groups. Therefore, it is suggested that three different supplements following the one RDA concept for all micronutrients be developed for research use in developing countries for the following age groups; 1 to 3 years, 4 to 13 years, and females > 14 years (excluding during pregnancy).

Publication Types:
* Review
* Review, Tutorial

PMID: 14564938 [PubMed - indexed for MEDLINE]

7. Kaluski DN, Tulchinsky TH, Haviv A, Averbuch Y, Rachmiel S, Berry EM, Leventhal A. Addition of essential micronutrients to foods--implication for public health policy in Israel. Isr Med Assoc J. 2003 Apr;5(4):277-80.

Food and Nutrition Services, Ministry of Health, Jerusalem, Israel. tropic@netvision.net.il

Micronutrient deficiencies have reoccupied the center stage of public health policy with the realization that folic acid deficiency results in neural tube defects and possibly other birth defects as well as ischemic heart disease. These, in turn, have raised an older debate on food fortification policy for the elimination of iodine, iron and vitamin D deficiencies. Data from the First Israeli National Health and Nutrition Survey (MABAT 2000) provided an impetus to develop an active national nutrition policy aimed to improve the nutritional status of iodine, iron, vitamins A and D and B-vitamins, including folate. In this paper we examine some of the micronutrient deficiency issues in Israel and their implications for public health, and suggest options for the formulation of policy.

PMID: 14509134 [PubMed - indexed for MEDLINE]

8. Navarro M, Wood RJ. Plasma changes in micronutrients following a multivitamin and mineral supplement in healthy adults. J Am Coll Nutr. 2003 Apr;22(2):124-32.

Mineral Bioavailability Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111, USA. nalarcon@platon.ugr.es

OBJECTIVE: To estimate the micronutrient (riboflavin, folate, vitamin C, vitamin B(12), iron, zinc and copper) bioavailability in healthy adults from a multi-micronutrient dietary supplement to assess the possible influence on it by the tablet disintegration properties and by the relative intestinal permeability of subject. METHODS: The bioavailability of seven micronutrients from a single brand of multi-micronutrient dietary supplement was measured on two separate occasions in the presence of a standardized test meal in 15 healthy adult subjects. Each subject visited the Metabolic Research Unit on four separate randomized occasions for an absorption test. One test measured the intestinal permeability. The other three tests measured the postprandial changes in plasma or serum concentrations after consuming a test meal alone (control:placebo effect), or the test meal with either whole or crushed and powdered dietary supplements. 15 healthy Caucasian adult volunteers, aged 42 +/- 14 years. RESULTS: The 12 hour-post-dose AUC for riboflavin, folate and vitamin C (whole and crushed tablet), and that for vitamin B(12) (only for the crushed tablet treatment) and iron (only for the whole tablet treatment) were all significantly ($p < 0.001$) higher than after a test meal alone. In contrast there was no significant increase in the AUC after supplement intake for zinc and copper. Neither the form of the supplement for all micronutrients tested nor intestinal permeability of the subject for riboflavin, folate, vitamin C, iron, zinc and copper influenced the postdose nutrient AUC. In contrast, for vitamin B(12) the intestinal permeability of the subject influenced significantly the nutrient AUC ($p = 0.003$). CONCLUSION: Tablet disintegration characteristics of this dietary supplement did not limit absorption of these seven micronutrients. The intestinal permeability of subject was only positively correlated with the B(12) bioavailability. Results are suggestive of using multi-micronutrients dietary supplements as a vehicle to decrease the prevalence of multiple micronutrient deficiencies overall for vitamins in healthy adults.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 12672708 [PubMed - indexed for MEDLINE]

Today, we see one or more of these issues as major factors affecting everyone. Stress, on its own, is a significant issue, but when we consider some of its related effects, such as loss of concentration, irritability, and health problems, then we see stress as being a key factor in many of the social problems facing people today.

Using nutrients for promoting health is not new to many practitioners who have studied the scientific literature and have had clinical experience in the use of supplements witnessing its benefits.

1. Cleghorn GJ. "We are what we eat". Asia Pac J Clin Nutr. 2004;13(Suppl):S29.

Department of Paediatrics and Child Health, University of Queensland, Royal Children's Hospital, Herston, Brisbane, Australia.

Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life. When considering any aspect of nutrition it should be possible to examine both the macro and micronutrient implications. Over the past few years there has been significant advance made in the provision of macronutrients and hence energy in an attempt to improve infant mortality and reduce protein energy malnutrition. Yet the continued lack of food does still result in significant stunting and wasting in many parts of the world. During the recent World Summit, both the World Health Organisation and UNICEF, have targeted micro nutrient deficiency, in particular, iodine deficiency, vitamin A deficiency and iron deficiency. They have set international goals to reduce and or eradicate these nutritional deficiencies. Each of these will be discussed in some detail in particular in their respective relationships with subsequent neurological development. Evidence will be shown to relate each of these areas to a common thread, namely, to myelin production and its effect on nerve conduction and subsequent development. There has also been considerable interest over the past few years in the relationship between perinatal and infant nutrition and subsequent adult disease patterns. Studies by Barker & others have shown that small body size at birth and during infancy are associated with increased rates of coronary heart disease and its major biological risk factors: - raised blood pressure, - impaired glucose tolerance and - abnormalities in lipid metabolism and - blood coagulation These findings led to the fetal origins hypothesis, which proposes that coronary heart disease originates through fetal adaptations to under nutrition.

PMID: 15294491 [PubMed - in process]

2. Biesalski HK, Brummer RJ, Konig J, O'Connell MA, Ovesen L, Rechkemmer G, Stos K, Thurnham DI. Micronutrient deficiencies. Hohenheim Consensus Conference. Eur J Nutr. 2003 Dec;42(6):353-63.

Dept. of Biological Chemistry and Nutrition, University of Hohenheim, Fruwirthstr. 12, 70593, Stuttgart, Germany.

OBJECTIVE: The aim of this study was to consider the risk of micronutrient deficiencies and approaches for intervention, and to summarize existing knowledge and identify areas of ignorance. DESIGN: Experts from a range of relevant disciplines received and considered a series of questions related to aspects of the topic. INTERVENTION: The experts met and discussed the questions and arrived at a consensus. CONCLUSION: Though healthy balanced diet is available for the general European population, a few defined groups are at risk of micronutrient deficiencies. In addition, the intake of specific micronutrients such as iron, folic acid, vitamin D and vitamin B12 are often marginal. To overcome these deficiencies, either selected micronutrients or a mixture of different micronutrients might be recommended. However, to define and detect micronutrient deficiencies, specific biomarkers are only available for a few micronutrients (e. g. vitamin D, folic acid, vitamin C, iron). The definition of a risk group, based on scientific data, might be an appropriate way to justify intervention with supplements.

Publication Types:
* Consensus Development Conference
* Review

PMID: 14673609 [PubMed - indexed for MEDLINE]

3. Ganji V, Hampl JS, Betts NM. Race-, gender- and age-specific differences in dietary micronutrient intakes of US children. Int J Food Sci Nutr. 2003 Nov;54(6):485-90.

Department of Consumer and Family Studies/Dietetics, San Francisco State University, San Francisco, CA 94132, USA. vijay@sfsu.edu

Race-, gender- and age-specific differences in dietary micronutrient intakes of 1- to 10-year-old US children were evaluated. Three-day, dietary intakes from the US Department of Agriculture's Continuing Survey of Food Intakes by Individuals were evaluated. Data from 1895 children (967 males, 928 females; 1,540 Whites, 355 Blacks) who resided in the 48 conterminous states were analyzed. Micronutrient intakes, intakes as percent of the Recommended Dietary Allowance (RDA) and percent of children who consumed < or =67% of the RDA were computed. Black males compared with White males, Black females compared with White females and White females compared with White males had significantly lower dietary intakes for several micronutrients. More Black males than White males had intakes < or =67% of the RDA for vitamin E, calcium and zinc. Blacks and female children were at a greater risk for vitamin A, vitamin E, calcium, iron and zinc deficiency.

PMID: 14522694 [PubMed - indexed for MEDLINE]

4. Oken E, Duggan C. Update on micronutrients: iron and zinc. Curr Opin Pediatr. 2002 Jun;14(3):350-3.

Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.

The past few years have seen several substantial advances in our understanding of the importance of micronutrients in child health and nutrition. Although historically child nutrition in developing countries has focused on protein and energy sufficiency, more recent efforts have been made to evaluate and eliminate micronutrient deficiencies. Accumulating data have underlined the important long-

term health effects that may occur with iron deficiency, and studies continue to confirm the benefits of successful treatment of iron deficiency anemia. Zinc is another micronutrient whose significance to child health is increasingly appreciated. Although breakthroughs in micronutrient research have generally come from populations in developing countries, children in industrialized countries also benefit from increasing knowledge about nutritional requirements and interventions.

Publication Types:
* Review
* Review, Tutorial

PMID: 12011679 [PubMed - indexed for MEDLINE]

In the last several years, however, vitamin research has become even more intriguing, attracting a segment of researchers involved with gene expression and gene modulation. What some people call metabolic tune up and DNA repair.

1. Ames BN. The metabolic tune-up: metabolic harmony and disease prevention. J Nutr. 2003 May;133(5 Suppl 1):1544S-8S.

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An optimum intake of micronutrients and metabolites, which varies with age and genetic constitution, would tune up metabolism and give a marked increase in health, particularly for the poor and elderly, at little cost. 1) DNA damage. Inadequate intake of folic acid causes millions of uracils to be incorporated into the DNA of each cell with associated chromosome breaks, essentially producing a radiation mimic. Deficiencies of the metabolically connected vitamins B-6 and B-12, which are also widespread, also cause uracil incorporation and chromosome breaks. Inadequate iron intake (2 billion women in the world; 25% of U.S. menstruating women) causes oxidants to leak from mitochondria and damages mitochondria and mitochondrial DNA. Inadequate zinc intake (approximately 10% in the U.S.) causes oxidation and DNA damage in human cells. 2) The K(m) concept. Approximately 50 different human genetic diseases that are due to a poorer binding affinity (K(m)) of the mutant enzyme for its coenzyme can be remedied by feeding high-dose B vitamins, which raise levels of the corresponding coenzyme. Many polymorphisms also result in a lowered affinity of enzyme for coenzyme. 3) Mitochondrial oxidative decay with age. This decay, which is a major contributor to aging, can be ameliorated by feeding old rats the normal mitochondrial metabolites acetyl carnitine and lipoic acid at high levels. They restore the K(m) for acetyl carnitine transferase and the velocity of the reaction as well as mitochondrial function; reduce levels of oxidants, neuron RNA oxidation and mutagenic aldehydes; and increase old-rat ambulatory activity and cognition.

Publication Types:
* Lectures

PMID: 12730462 [PubMed - indexed for MEDLINE]

2. Ames BN. A role for supplements in optimizing health: the metabolic tune-up. Arch Biochem Biophys. 2004 Mar 1;423(1):227-34.

Children's Hospital Oakland Research Institute, CA 94609, USA. bruceames@chori.org

An optimum intake of micronutrients and metabolites, which varies with age and genetic constitution, would tune up metabolism and give a marked increase in health, particularly for the poor, young, obese, and elderly, at little cost. (1) DNA damage. Deficiency of vitamins B-12, folic acid, B-6, C or E, or iron or zinc appears to mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions or both. Half of the population may be deficient in at least one of these micronutrients. (2) The Km concept. Approximately 50 different human genetic diseases that are due to a poorer binding affinity (Km) of the mutant enzyme for its coenzyme can be remedied by feeding high-dose B vitamins, which raise levels of the corresponding coenzyme. Many polymorphisms also result in a lowered affinity of enzyme for coenzyme. (3) Mitochondrial oxidative decay. This decay, which is a major contributor to aging, can be ameliorated by feeding old rats the normal mitochondrial metabolites acetyl carnitine and lipoic acid at high levels. Many common micronutrient deficiencies, such as iron or biotin, cause mitochondrial decay with oxidant leakage leading to accelerated aging and neural decay.

Publication Types:
* Review
* Review, Tutorial

PMID: 14989256 [PubMed - indexed for MEDLINE]

3. Fenech M. Micronutrients and genomic stability: a new paradigm for recommended dietary allowances (RDAs). Food Chem Toxicol. 2002 Aug;40(8):1113-7.

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Diet as a key factor in determining genomic stability is more important than previously imagined because we now know that it impacts on all relevant pathways, namely exposure to dietary carcinogens, activation/detoxification of carcinogens, DNA repair, DNA synthesis and apoptosis. Current recommended dietary allowances for vitamins and minerals are based largely on the prevention of diseases of deficiency such as scurvy in the case of vitamin C. Because diseases of development, degenerative disease and aging itself are partly caused by damage to DNA it seems logical that we should focus better our attention on defining optimal requirements of key minerals and vitamins for preventing damage to both nuclear and mitochondrial DNA. To date, our knowledge on optimal micronutrient levels for genomic stability is scanty and disorganised. However, there is already sufficient evidence to suggest that marginal deficiencies in folate, vitamin B12, niacin and zinc impact significantly on spontaneous chromosome damage rate. The recent data for folate and vitamin B12 in humans with respect to micronucleus formation in blood and epithelial cells provide compelling evidence of the important role of these micronutrients in maintenance of genome integrity and the need to revise current RDAs for these micronutrients based on minimisation of DNA damage. Appropriately designed in vitro studies and in vivo placebo controlled trials with dose responses using a complementary array of DNA damage biomarkers are required to define recommended dietary allowances for genomic stability. Furthermore these studies would have to be targeted to individuals with common

genetic polymorphisms that alter the bioavailability of specific micronutrients and the affinity of specific key enzymes involved in DNA metabolism for their micronutrient co-factor. That there is a need for an international collaborative effort to establish RDAs for genomic stability is self-evident..

Publication Types:
* Review
* Review, Tutorial

PMID: 12067572 [PubMed - indexed for MEDLINE]

4. Fenech M. Genome health nutrigenomics: nutrition and the science of optimal genome maintenance. Asia Pac J Clin Nutr. 2004;13(Suppl):S15.

CSIRO Health Sciences and Nutrition, Adelaide, South Australia.

The link between genome instability and adverse health outcomes during the various stages of life, such as infertility, foetal development, cancer and neurodegenerative disease is compelling. This will be reviewed against a background of evidence indicating that genome instability, in the absence of overt exposure of genotoxins, is itself a sensitive marker of nutritional deficiency. The latter will be illustrated with cross-sectional and dietary intervention data obtained using the micronucleus assay, an efficient biomarker for diagnosing genome instability (chromosome breakage, chromosome rearrangement, gene amplification and aneuploidy) and nutritional deficiency. The concept of recommended dietary allowances for genome stability and how this could be achieved will be discussed together with the emerging field of nutritional genomics for genome stability. With regards to the latter we have shown that the MTHFR C677T polymorphism and riboflavin (the cofactor for MTHFR) have a significant effect on genome instability, however, the effect is relatively small when compared to folic acid. In addition this study has shown that excess riboflavin enhances the genome damaging effect of folic acid deficiency indicating the importance of nutrient-nutrient as well as gene-nutrient interaction. It is evident from initial studies that optimal concentration of micronutrients for prevention of genome and epigenome (i.e. CpG methylation in DNA) damage is dependent on genetic polymorphisms that alter function of genes involved directly or indirectly in DNA metabolism and repair. The lecture concludes with a vision for an alternative disease prevention strategy based on the diagnosis and nutritional treatment of genome instability depending on an individual's genetic background i.e. Genome Health Clinics.

PMID: 15294477 [PubMed - in process]

5. Wei Q, Shen H, Wang LE, Duphorne CM, Pillow PC, Guo Z, Qiao Y, Spitz MR. Association between low dietary folate intake and suboptimal cellular DNA repair capacity. Cancer Epidemiol Biomarkers Prev. 2003 Oct;12(10):963-9.

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Both reduced DNA repair capacity (DRC) and folate deficiency are associated with increased cancer risk. Furthermore, folate is involved in DNA repair through de novo DNA synthesis and methylation. To determine whether low dietary folate intake is associated with low cellular DRC in humans, we assessed total dietary folate intake using a food frequency questionnaire in 559 non-Hispanic white

cancer-free subjects enrolled from 1995 through 2001 as controls for ongoing molecular epidemiological studies from among enrollees in a community-based multispecialty physician practice in the Houston metropolitan area. We assessed cellular DRC using the host-cell reactivation assay that measures nucleotide-excision repair capacity in peripheral blood lymphocytes. The distribution of DRC was approximately normal in this study population. In univariate analysis, subjects in the lowest tertile of total dietary folate intake (<170 microg/1000 kcal/day) exhibited a significant reduction (-18%) in DRC compared with those in the upper tertile (>225 microg/1000 kcal/day; P < 0.001). In multivariate linear regression analysis, calorie-adjusted total folate intake remained an independent predictor of DRC (P < 0.001). Additional stratification analysis indicated that this association was more pronounced in those who did not use folate supplementation (n = 230; P < 0.001) compared with those who did (n = 329; P = 0.177). Our findings suggest that low dietary folate intake is associated with suboptimal cellular DRC. Once replicated by other investigators, this finding has public health implications by reinforcing the need for folate supplementation or dietary modification for the at-risk population.

PMID: 14578130 [PubMed - indexed for MEDLINE]

By "cracking" the human genome, scientists thought that they would have the answer to all our problems, both physical and mental. Considerable funding was diverted to this endeavour. However, researchers found that gene manipulation was not that simple. Experiments inserting a "normal" gene in place of a defective one did not work . What they did not take into account in their experiments was the effect of the environment. Another branch of science was in charge of that field. It's called "Epigenetics."

In 1990, the first human gene therapy experiment was performed by Dr. French Anderson, Director of gene therapy at the University of southern California's medical school. It was successfully performed on a young four-year old girl. However, by 1996, gene experiments in over 3,000 participants mostly ended in tragedy, according to Dr. Anderson.[1]

Scientists began to realize that replacing defective genes with healthy ones wasn't the only way to manipulate them. Researchers in the growing field of epigenetics found that simple, food-based, methyl groups from folic acid, choline, B-12, and B-6 can turn on or off genes because methylation can either increase or decrease the level of RNA transcription.[2] These same nutrients, folic acid, B-12 and B-6 were recently found to be necessary in preventing homocysteine build up and consequent heart disease.[3-13]

In one epigenetic review paper authors noted that folate was the most extensively studied nutrient in DNA synthesis and repair, and maintenance of DNA methylation.[14] Epigenetic research gave a mechanism for the action of folate in the prevention of spinal cord defects.[15] In another study on dietary requirements and possible effects on DNA methylation, the authors commented on the importance of the interchangeable nature of methionine, methyl-tetrahydrofolate, and choline as sources of methyl groups and not just focusing on one nutrient.[16] In one epigenetic study, researchers concluded that, "Optimum dietary supplements for the health and longevity of offspring should be intensively investigated. This should lead to public policy guidance that teaches optimal, rather than minimal, dose levels of maternal supplements."[17]

In this burgeoning field of epigenetics a 2003 study showed that, "Early nutrition affects adult metabolism in humans and other mammals, potentially via persistent alterations in DNA methylation."[18] In this study researchers proved that a diet rich in methyl groups turned off a gene that led to adult obesity and diabetes in mice. It's not so much the fault of the genes in these conditions but to what nutrient broth the genes are exposed. One of the authors said that, "Methylation is nature's way of allowing environmental factors to tweak gene expression without making permanent mutations." Methyl groups are entirely derived from the foods people eat and the supplements they ingest. They include vitamin B12, folic acid, and choline.

To sum up, Jean-Pierre Issa, a researcher at Anderson Cancer Center in Texas, found considerable variation in the degree of methylation among individuals with colitis, cirrhosis, and cancer. In one paper he wrote that environmental exposures leading to inflammation could account for part of the epigenetic variation in human populations, probably by draining the body of necessary vitamin and mineral cofactors. His concluding statement was that epigenetic variation related to aging, lifestyle, exposures and possibly genetic factors, is one of the modulators of acquired, age-related human diseases, including cancer.[19]

Scientific proof for the absolute need for essential nutrients in our diet comes at a time when children and adults are mostly eating fast food and junk food. According to a report from The Center for Science in the Public Interest, wrote and says "Food Companies Undermine Parents, Overfeed Kids" (see Appendix B) children have an inadequate intake of good food. Children overeat high caloric soft drinks and high carbohydrate food and become overweight. They also develop malnutrition from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

The same can be said for adults who aren't eating their vegetables either. In a 2004 poll of 2,472 Americans, by AC Nielsen, more than 85% of consumers are not eating the federally recommended minimum of five servings of produce a day. The poll was commissioned by "Produce for Better Health Foundation", a non-profit nutrition education group funded by the produce industry.[20]

The ingredients in VitaMind™ number thirty-one. The formula encompasses those vital vitamins, minerals, fatty acids, amino acids, and herbs that have been proven to assist and support normal mental functions and mood stability. They include the important nutrients that contain methyl groups: vitamin B12, folic acid, and choline.

DOSAGE AND SAFETY

All VitaMind™ nutrients are well within the Recommended Daily Allowance (RDA) and Upper Limit (UL) as seen on Chart in Appendix A.

The dosage of VitaMind™ is 2 capsules taken morning and evening with food.

As with any new supplement, it is best to begin with one a day and every two days increase by one more capsule. After several weeks on the supplement, most people cut back to one capsule morning and one capsule in the evening.

References from the scientific literature on each ingredient in VitaMind™ can be found at the end of each ingredient section.

While the emphasis of scientific research seems to be to find a patentable way of taking over the function of natural body processes, there is still much research on the basic nutrients that the body needs. For example, the B vitamin, niacin, acts as a necessary co-enzyme in over 500 metabolic functions in the body.

Scientific evidence shows that there is:

1. Nutrient deficiency in various populations
2. The need for supplement complexes and not single supplements
3. The nutrient requirement for mind and mood balance

MODERN MEDICAL VIEW OF NUTRIENTS

Doctors make several assumptions about nutrients and diet.

1. That we are vitamin replete.
2. That our diets are adequate.
3. That we suffer no vitamin deficiency diseases—because doctors claim not to see cases of scurvy, pellagra, and beri beri.

They make these assumptions based on the fact that they view vitamins as only important to prevent frank vitamin deficiency disease. In the history of vitamin discovery and usage there are two views of what they are and how they should be used among researchers and medical doctors.

VITAMINS-AS-PREVENTION

According to Dr. Abram Hoffer, who has studied and used nutrients in hospital-based work and private practice for over fifty years, there is the Vitamins-as-Prevention paradigm—that is, to prevent frank vitamin deficiency disease and Vitamins-as-Treatment, which takes into account the burgeoning research in the beneficial aspects of vitamins on treating and preventing disease.[21]

- ♥ Vitamin C is necessary to prevent scurvy
- ♥ Thiamine (Vitamin B-1) prevents beri beri
- ♥ Vitamin D prevents rickets
- ♥ Niacin (Vitamin B-3) prevents pellagra

It was argued by early researchers that if you merely want to prevent frank deficiency symptoms you only need the above vitamins in small amounts—which was eventually translated into the RDA. The RDA says nothing about optimal dose; it is an amount that can only stave off frank deficiency.

This type of thinking about vitamin usage dictated that since vitamins were only needed in small amounts to prevent deficiency, then large doses of vitamins were contraindicated and may be dangerous. Dr. Hoffer remarks that "the evidence for this is non existent, and indicates that the clinician is probably not fit to practice medicine." Dr. Hoffer confirms that the unfortunately Vitamin-as-Prevention paradigm is the one accepted by almost every nutritionist, physician, hospital, government agency, and food board in the Western world.

VITAMINS-AS-TREATMENT

Vitamins-as-Treatment goes beyond supplementing to prevent deficiency and finds that vitamins are therapeutic for a large number of conditions not considered to be vitamin deficiency diseases. Optimum doses are used that vary from small to large but are much larger than the ones recommended by the original paradigm and by the RDA.

An example that Dr. Hoffer gives is niacin, which, when used in 3 to 9 grams dosages daily lowers total cholesterol, elevates high-density lipoprotein cholesterol, and lowers elevated triglycerides. This unexpected property of niacin was reported in 1955 and marks the beginning of the new Vitamins-as-Therapy paradigm. Before that time Vitamin E was found to be useful in treating and preventing heart disease. Niacinamide was helpful in arthritic conditions, and Vitamin C in high doses was found to be very therapeutic for a large number of conditions including cancer, viral and bacterial infections, and multiple sclerosis. However, because the paradigm of Vitamins-as-Prevention was in "power" any use of vitamins beyond small doses was ridiculed.

Vitamins and minerals are co-factors in thousands of metabolic functions in the body. Even though the vast majority of doctors and dieticians claim that we can meet all our vitamin needs in your diet—that is decidedly not the case. Vitamin studies always show a deficiency in a high proportion of the population. If the RDAs were meeting our needs we should not have deficiency. Therefore, we presently have a situation in our society where we have a deficiency of vitamins and also a need for vitamins on a therapeutic level—neither of which Health Canada is considering. If Health Canada continues to listen to the prevailing Vitamins-as-Prevention lobby and continues to judge some vitamins as dangerous and all vitamins only in the RDA we will have an outright epidemic of chronic disease.

VITAMINS ARE NON-TOXIC

From Abram Hoffer MD PhD, "Over-the-counter Drugs" in the Journal of Orthomolecular Medicine, May 2003.

"Any discussion of side effects or of toxic reactions without specifying the doses of these compounds is meaningless. For at zero levels nothing is and at high enough levels everything is toxic including oxygen and water. Critics of optimum (often high) doses of vitamins generally talk about toxic reactions without any reference to the doses that people use. They report that vitamins may be toxic. They do not write will be harmful because the word may is a very useful term as it means little

and can be used to appear to be very scientific. How often have we seen …headlines (that) vitamin C may be harmful, may cause cancer and so on. For example one of the well entrenched fictions is that vitamin C may cause kidney stones. This is not based on fact. There are no reports in the worldwide literature, which prove that this is true, and there are many good studies that show that it is not true. Yet the statement has developed a life of its own which is not anchored by any observation of facts…Millions of people take vitamin C. So far not one finding has established this as fact. So in discussing side effects and toxicity we must always use the simplest most accurate language possible referring to the doses being discussed."

HEALTH CANADA VIEWS VITAMINS AS PREVENTING DEFICIENCY DISEASE

Health Canada knows the existing research—but by assuming that there is risk to vitamins and painting them with the same brush as drugs, it is erring on the side of caution in assigning risk to nutrients that we are deficient in.

COMPARING DEATHS DUE TO NUTRIENTS AND DEATHS DUE TO DRUGS

There are an average of 1 or 2 deaths due to nutrients annually in North America, whereas up to 784,000 people die annually in the US due to iatrogenesis-the disease caused by medical treatment.[22]

The 1998 study by Lazarou and Pomeranz found that 2.2 million people are injured and 106,000 people die annually in the U.S. due to properly prescribed drugs. These are the drugs to which risk assessment must be applied.[23]

THE PRECAUTIONARY PRINCIPLE

The Precautionary Principle is being adopted in Europe regarding the use of chemicals and drugs. According to Jeremy Rifkin of the UK Guardian, May 12, 2004, "a proposed EU directive…would force companies to prove chemical products introduced into the marketplace are safe before being granted permission to market them. Existing laws allow most chemical-based products to be introduced without prior assurances by the company of their safety. The result is that 99% of the total chemicals sold in Europe have not passed through any environmental and health testing review process.." The opposite "principle" should be applied to the use of Vitamins-as-Treatment. In other words, we know enough about the safety of vitamins and their absolute requirement for maintaining a healthy body, therefore we must be able to use them freely without imposition of punitive low dosage levels. We presently know as much as we need to know to begin supplementing with much larger than the RDAs of most nutrients.

DOCTORS DO NOT LEARN ABOUT NUTRITION

Because of the assumption that all nutrient needs are met by the diet, medicine has spent no time on nutrient education. This is part of the reason why we have an epidemic of heart disease that is in part due to lack of the B vitamins necessary to break down protein—when they don't there is a build up of homocysteine that causes heart and blood vessel damage. It's a simple vitamin deficiency that has been missed, overlooked, and ignored by modern medicine, funded by drug companies to find drug solutions to what is turning out to be an epidemic of nutrient deficiency diseases. See VitaMind™ References at the end of each ingredient section.

INTRODUCING THE STRAUSS QUESTIONNAIRES

When using any pill, supplement or drug, there is always the issue of patient compliance. To assist you in generating patient compliance, in order for patients to obtain the maximum benefit from VitaMind™, we offer you the following questionnaire. It is designed for two follow up visits, at your discretion. When a patient first fills out the questionnaire, they can easily identify the major stresses in their life that may be affecting their mental state. Knowing that they will be filling out the questionnaire on subsequent visits tends to make patients compliant to the supplement and enhances their outcome.

We suggest printing the questionnaire in triplicate. You may give one to your patient so they can identify their stresses in the future, one is for their chart, and we would appreciate if you would return the third copy to Strauss Herb Company at 755 Fortune Drive, Kamloops, BC V2B 2L3.

At Strauss Herb Co. we are committed to spending the time and the money to do research on natural supplements. The VitaMind™ Questionnaire will become part of a clinical outcomes trial on our products. Such research will not only serve Strauss Herb Co. but the natural products industry as a whole.

EVALUATION QUESTIONNAIRES

STRAUSS MOOD QUESTIONNAIRE

This test can be completed before going on a program that includes VitaMind™ and again after 2 months on the program to assess your ability to handle stress.

Everybody has experienced the following feelings or habits. What helps decide whether or not your stress levels are affecting your moods is whether you answer yes to more than 8 of the following questions. You do not have to indicate your responses beside each question, just add up the total number for which you would honestly answer yes.

After going on a program that includes taking VitaMind™, your doctor will ask you to fill out this questionnaire again and follow your ability to handle stress so that it doesn't impact negatively on your mood and daily living.

1. Have you lost interest in your family, friends, work, hobbies and/or activities?
2. Are you in conflict with family members, friends, and/or co-workers?
3. Do you cry easily?
4. Do you hold in your feelings?
5. Are you more irritable lately?
6. Do you tend to overreact?
7. Are you quick to anger?
8. Do you feel lonely?
9. Would you describe yourself as feeling miserable and sad, unhappy or blue?
10. Do you find it hard to make the best of difficult situations?
11. Do you get jealous of other people or their possessions?
12. Do you have sleep problems—too much or too little sleep?
13. Have you experienced changes in your appetite and/or weight?
14. Are you unable to think clearly or concentrate?
15. Is it difficult to make decisions and/or clarify and achieve your goals?
16. Do you feel you are under too much pressure?
17. Are you gambling?
18. Are you drinking more alcohol, coffee, and/or smoking cigarettes?
19. Are you using street drugs?
20. Are you sick more often than usual?
21. Do you have frequent episodes of diarrhea or constipation?
22. Do you have frequent headaches?
23. Do you hear your heart beating in your ears?
24. Do you drink alcohol every day?

THE STRAUSS SOCIAL READJUSTMENT RATING SCALE (SSRRS)

This is a test done once a year to assess the stress levels of patients.

Directions: Review the last year and the Life Events/Challenges that occurred. If two life events or challenges occurred, for example, death of two close family members, multiply the Score by two. Add up your score and compare with the scale below.

	Life Event/Challenge	Scoring	My Score
1.	Death of spouse	100	_____
2.	Divorce	73	_____
3.	Marital separation	65	_____
4.	Jail term	63	_____
5.	Death of close family member	63	_____
6.	Car accident	60	_____
7.	Personal injury or illness	53	_____
8.	Caring for an ailing or aging family member	53	_____
9.	Marriage	50	_____
10.	Fired from work	47	_____
11.	Marital reconciliation	45	_____
12.	Retirement	45	_____
13.	Change in health of family member	44	_____
14.	Pregnancy	44	_____
15.	Sex difficulties	39	_____
16.	Gain of new family member	39	_____
17.	Business readjustment	39	_____
18.	Change in financial state	38	_____
19.	Death of close friend	37	_____
20.	Change to different line of work	36	_____
21.	Change in number of arguments with spouse	35	_____
22.	Not sleeping well more than 3 nights a week	35	_____
23.	Mortgage over $25,000	31	_____
24.	Foreclosure of mortgage or loan	30	_____
25.	Watch 2+ hours of TV per day	30	_____
26.	Spend 2+ hours on the internet per day	30	_____
27.	Work more than 40 hours per week	30	_____

(Cont'd on next page)

28.	Expressing addictive behavior (more than 3 alcoholicbeverages; more than 20 cigarettes; more than 3 coffees per day)	30	_____
29.	Gambling on a regular basis	30	_____
30.	Experiencing road rage	30	_____
31.	Change in responsibilities at work	29	_____
32.	Son or daughter leaving home	29	_____
33.	Trouble with in-laws	29	_____
34.	Outstanding personal achievement	28	_____
35.	Spouse begins or stops work	26	_____
36.	Begin or end school	26	_____
37.	Change in living conditions	25	_____
38.	Taking one or more medications	25	_____
39.	Revision of personal habits	24	_____
40.	Trouble with boss	23	_____
41.	Change in work hours or conditions or pay	20	_____
42.	Read the newspaper daily	20	_____
43.	Change in residence	20	_____
44.	Change in schools	20	_____
45.	Change in recreation	19	_____
46.	Change in church activities	19	_____
47.	Change in social activities	18	_____
48.	Mortgage or loan less than $25,000	17	_____
49.	Change in sleeping habits	16	_____
50.	Change in number of family get-togethers	15	_____
51.	Change in eating habits	15	_____
52.	Vacation	13	_____
53.	Christmas activities	12	_____
54.	Minor violation of the law	11	_____

Total Score_____

Updated from the Social Readjustment Rating Scale (SRRS) Source: Holmes TH, Rahe RH. The Social Readjustment Rating Scale. Journal of Psychosomatic Research, II, p. 216. 1967.

Stress Scale: Scores below 150: 20% in this range become ill in the near future. Scores between 150-299: 50% in this range become ill in the near future. Scores over 300: 80% in this range become ill in the near future.

VITAMIND™ INGREDIENTS

VITAMIN A (RETINYL PALMITATE)

Studies have shown an association between vitamin A deficiency or imbalance and mental and psychomotor development[1,2] and cognitive function[3,4].

The following description of Vitamin A is taken from The Merck Manual of Diagnosis and Therapy (Seventeenth Edition).

VITAMIN A DEFICIENCY

Vitamin A (retinol) is fat soluble and is found mainly in fish liver oils, liver, egg yolks, butter, and cream. Green leafy and yellow vegetables contain -carotene and other provitamin carotenoids, which are converted to retinal in the mucosal cells of the small intestine. Retinal is reduced to retinol, then esterified. Most of the body's vitamin A is stored in the liver as retinyl palmitate. It is released into the circulation as retinol bound to retinol binding protein and prealbumin (transthyretin). The 11-*cis* isomer of retinal (vitamin A aldehyde) combines with opsin to form rhodopsin, the prosthetic group of photoreceptor pigments in the retina. In somatic cells, retinol is converted to retinoic acid, which combines with receptors that bind to DNA and regulate gene expression to maintain epithelial tissues and guide differentiation of a variety of other tissues.

Biologic equivalents, for diets with different proportions of retinol and -carotene, are as follows: 1 USP U equals 1 IU; 1 IU equals 0.3 μg of retinol; 1 μg of -carotene equals 0.167 μg of retinol. Other provitamin carotenoids are half as active as -carotene.

Synthetic vitamin analogs (retinoids) are used increasingly in dermatology. The possible protective role of -carotene, retinol, and retinoids against some epithelial cancers is under investigation.

ETIOLOGY

Primary vitamin A deficiency is usually caused by prolonged dietary deprivation. It is endemic in areas, such as southern and eastern Asia, where rice, devoid of carotene, is the staple.

Secondary vitamin A deficiency may be due to inadequate conversion of carotene to vitamin A or to interference with absorption, storage, or transport of vitamin A. Interference with absorption or storage is likely in celiac disease, sprue, cystic fibrosis, pancreatic disease, duodenal bypass, congenital partial obstruction of the jejunum, obstruction of the bile ducts, giardiasis, and cirrhosis. Vitamin A deficiency is common in protein-energy malnutrition (marasmus or kwashiorkor), principally because the diet is deficient but also because vitamin A storage and transport are defective.

Symptoms and Signs

The severity of the effects of vitamin A deficiency is inversely related to age. Growth retardation is a common sign in children. Inadequate intake or utilization of vitamin A can cause impaired dark adaptation and night blindness; xerosis of the conjunctiva and cornea; xerophthalmia and keratomalacia; keratinization of lung,

GI tract, and urinary tract epithelia; increased susceptibility to infections; and sometimes death. Follicular hyperkeratosis of the skin is common.

Pathognomonic changes are confined to the eye (see Keratomalacia in Ch. 96). The earliest change, rod dysfunction, can be detected by dark adaptometry, rod scotometry, or electroretinography (these tests require cooperative subjects). Dysfunction of the retina is followed by changes in the structure and function of epithelial cells. Xerosis of the bulbar conjunctiva consists of drying, thickening, wrinkling, and muddy pigmentation; the cornea becomes xerotic, infiltrated, and hazy at an early stage. Keratomalacia rapidly supervenes with liquefaction of part or all of the cornea, leading to rupture, with extrusion of the eye contents and subsequent shrinking of the globe (phthisis bulbi), or to anterior bulging (corneal ectasia and anterior staphyloma) and blindness. **Bitot's spots** (superficial foamy patches composed of epithelial debris and secretions on the exposed bulbar conjunctiva) occur in advanced deficiency; they are most likely due to vitamin A deficiency when they occur in young children who have other indications of vitamin A deficiency. In severe vitamin A deficiency in children, mortality can be 50% or more.

Laboratory Findings and Diagnosis

Evidence of vitamin A depletion is unobtainable in the preclinical stage, except for a history of inadequate intake. Plasma retinol levels fall after liver stores are exhausted. The normal range is 20 to 80 μg/dL (0.7 to 2.8 μmol/L); 10 to 19 μg/dL (0.35 to 0.66 μmol/L) is low, and < 10 μg/dL (< 0.35 μmol/L) is deficient. Mean plasma retinol binding protein (RBP) is 47 μg/mL for adult males and 42 μg/mL for adult females. Up to the age of 10 yr, the range is 20 to 30 μg/mL. Plasma levels of vitamin A and RBP fall in deficiency states and in acute infections. Other causes of night blindness (eg, retinitis pigmentosa) must be excluded. Secondary infection may complicate the corneal changes. Trial with therapeutic doses of vitamin A assists in the diagnosis.

VITAMIN A DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation: Vitamin A (retinol) is fat soluble and is found mainly in fish liver oils, liver, egg yolks, butter, and cream. Green leafy and yellow vegetables contain -carotene and other provitamin carotenoids, which are converted to retinal in the mucosal cells of the small intestine.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." And as noted in the laboratory section of the Merck Manual citation: "Evidence of vitamin A depletion is unobtainable in the preclinical stage, except for a history of inadequate intake."

VITAMIN A TOXICITY

Excessive intake of vitamin A may cause acute or chronic toxicity. **Acute toxicity** in children may result from taking large doses (> 100,000 μg or 300,000 IU); it manifests as increased intracranial pressure and vomiting, which may lead to death unless ingestion is discontinued. After discontinuation, recovery is spontaneous, with no residual damage; only two fatalities have been reported. Within a few hours of ingesting several million units of vitamin A in polar bear or seal liver, arctic

explorers developed drowsiness, irritability, headache, and vomiting, with subsequent peeling of the skin. Megavitamin tablets containing vitamin A have occasionally induced acute toxicity when taken for a long time.

Chronic toxicity in older children and adults usually develops after doses of > 33,000 µg (100,000 IU)/day have been taken for months. In infants who are given 6,000 to 20,000 µg (20,000 to 60,000 IU)/day of water-miscible vitamin A, evidence of toxicity may develop within a few weeks. Birth defects have been reported in the children of women receiving 13-cis-retinoic acid (isotretinoin) for skin conditions during pregnancy (see Drugs in Pregnancy in Ch. 249).

Massive doses (50,000 to 120,000 µg or 150,000 to 350,000 IU) of vitamin A or its metabolites are given daily to persons with globular acne. Although the treatment is effective, it puts the patient at risk for vitamin A toxicity.

Although carotene is metabolized in the body to vitamin A at a slow rate, excessive ingestion of carotene does not cause vitamin A toxicity but produces **carotenemia** (carotene blood levels > 250 µg/dL [> 4.65 µmol/L]). This condition is usually asymptomatic but may lead to **carotenosis**, in which the skin (but not the sclera) becomes deep yellow, especially on the palms and soles. Carotenosis may also occur in diabetes mellitus, myxedema, and anorexia nervosa, possibly from a further reduction in the rate of conversion of carotene to vitamin A.

Symptoms, Signs, and Diagnosis

Sparse coarse hair, alopecia of the eyebrows, dry rough skin, and cracked lips are early signs. Later, severe headache, pseudotumor cerebri, and generalized weakness are prominent. Cortical hyperostosis and arthralgia are common, especially in children. Hepatomegaly and splenomegaly may occur.

Normal fasting plasma retinol levels range from 20 to 80 µg/dL (0.7 to 2.8 µmol/L). In vitamin A toxicity, fasting plasma levels may exceed 100 µg/dL (3.49 µmol/L), up to 2000 µg/dL (69.8 µmol/L). Differential diagnosis may be difficult because symptoms are varied and bizarre, but they usually include headache and rash.

Prognosis and Treatment

Prognosis is excellent for adults and children. Symptoms and signs usually disappear within 1 to 4 wk after stopping vitamin A ingestion. However, prognosis for the fetus of a mother taking megadoses of vitamin A is guarded.

VITAMIN A REFERENCES

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Southeast Asian Ministers of Education Organization, Tropical Medicine (SEAMEO TROPMED), Regional Centre for Community Nutrition, University of Indonesia, Jakarta, Indonesia.

Maternal nutrition is important for fetal development, but its impact on the functional outcome of infants is still unclear. The present study investigated the effects of vitamin A and Fe supplementation during gestation on infant mental and psychomotor development. Mothers of infants from five villages in Indonesia were

randomly assigned to supervised, double-blind supplementation once per week from approximately 18 weeks of pregnancy until delivery. Supplementation comprised 120 mg Fe+500 microg folic acid with (n 94) or without (n 94) 4800 microg retinol in the form of retinyl acetate. Mothers of infants who participated in the national Fe+folic acid supplementation programme, but whose intake of supplements was not supervised, were recruited from four other villages (n 88). The mental and psychomotor development of infants was assessed, either at 6 or 12 months of age, using the Bayley Scales of Infant Development (BSID). We found no impact of vitamin A supplementation on mental or psychomotor development of infants. In addition, infants whose mothers had received weekly Fe supplementation had similar mental and psychomotor indices as those whose mothers had participated in the governmental Fe supplementation programme. The study population was moderately Fe and vitamin A deficient. The size of the treatment groups was large enough to detect a mean difference of 10 points on the BSID, which is less than 1 sd (15 points) of the average performance of an infant on the BSID. In conclusion, the present study did not find an impact of weekly supplementation of 4800 RE vitamin A in addition to Fe during gestation on functional development of Indonesian infants. However, smaller improvements in development may be seen if studied in a larger and/or more deficient population.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

2. Singh M. Role of micronutrients for physical growth and mental development. Indian J Pediatr. 2004 Jan;71(1):59-62.

Child Care and Dental Health Center, Noida, UP, India.
meharban.s.singh@gsk.com

Due to control of florid and severe cases of protein-energy malnutrition, deficiencies of micronutrients in children have assumed public health importance. According to National Nutrition Monitoring Bureau of India, over 50% of apparently healthy looking children have subclinical or biochemical deficiencies of vitamin A, vitamins B2, B6, folate and vitamin C. Over two-third of children have clinical evidences of iron deficiency while deficiency of trace minerals like iodine and zinc is quite common in certain populations. Children have food preferences and they are quite fussy to take green leafy vegetables and fruits thus compromising their intake of micronutrients from dietary sources. The full genetic potential of the child for physical growth and mental development may be compromised due to subclinical deficiencies of micronutrients which are commonly referred to as "hidden hunger". Micronutrients are required for the integrity and optimal functioning of immune system. Children with subclinical deficiency of micronutrients are more vulnerable to develop frequent and more severe common day-to-day infections thus triggering a vicious cycle of undernutrition and recurrent infections. A number of micronutrients are required for optimal physical growth and neuromotor development. Isolated deficiencies of micronutrients are rare in clinical practice and usually deficiencies of multiple micronutrients co-exist. The first 3 years of life are most crucial and vulnerable to the hazards of undernutrition. All efforts should be made so that preschool children are given a balanced and nutritious home-based diet. However, it has been shown that it is not possible to meet 100% requirements of recommended dietary allowances (RDA's) of micronutrients from dietary sources

alone and most preschool children need administration of nutritional supplements to optimize their genetic potential for physical growth and mental development.

Publication Types:
* Review
* Review, Tutorial
PMID: 14979388 [PubMed - indexed for MEDLINE]

3. Kapil U, Bhavna A. Adverse effects of poor micronutrient status during childhood and adolescence. Nutr Rev. 2002 May;60(5 Pt 2):S84-90

Department of Human Nutrition, All India Institute of Medical Sciences, Ansari Nagar, New Delhi.

Despite India's substantial progress in human development since its independence in 1947, 5-7% of its children have vitamin A deficiency disorders in selected geographic areas, 53% have iron deficiency anemia, and 9% have goiter. Three micronutrients--vitamin A, iron, and iodine--are among the most important of all the nutrients needed by the body because they are vital for developing normal learning and cognitive functions, immunity, work capacity, and reproductive health. The body cannot synthesize them, so they must be made available through the diet. Deficiencies of these three micronutrients are known to have devastating effects on health.

Publication Types:
* Review
* Review, Tutorial

PMID: 12035866 [PubMed - indexed for MEDLINE]

4. Viteri FE, Gonzalez H. Adverse outcomes of poor micronutrient status in childhood and adolescence. Nutr Rev. 2002 May;60(5 Pt 2):S77-83.

Department of Nutritional Sciences and Toxicology, University of California at Berkeley, 94720, USA.

The adverse effects of micronutrient deficiencies and excesses in children up to reproductive age are presented. A summary of risks and adverse functional and health outcomes associated with deficient and excessive intakes and nutrition status of iron, iodine, zinc, vitamins A and D, folate, vitamin B12, and riboflavin is presented. Nutrient-nutrient interactions of micronutrients, age, gender, and other host and environmental conditions, such as pregnancy, genetic conditions, overall nutrition, force of infection, and social conditions are considered as covariates in trying to define causation and outcomes due to specific micronutrients. The outcomes analyzed focus on growth and development, mental and neuromotor performance, immunocompetence, physical working capacity, morbidity, and in the case of pregnancy, overall reproductive performance. The results presented include responses to specific and multiple "experimental" interventions. A brief analysis of possible public health programs is presented, with emphasis on prevention.

Publication Types:
* Review
* Review, Tutorial
PMID: 12035865 [PubMed - indexed for MEDLINE]

VITAMIN C (ASCORBIC ACID)

Vitamin C: Studies have shown an association between vitamin C deficiency or imbalance and aggression[1], anxiety[2,3], bipolar disorder[4,5,6], depression[4,7,8,9,10,11], schizophrenia[8,12,13], neurodegeneration[14], surgical stress[15], lowering cortisol[16], and memory[17].

The following description of Vitamin C is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

VITAMIN C DEFICIENCY

Vitamin C (ascorbic acid) is essential for collagen formation and helps maintain the integrity of substances of mesenchymal origin, such as connective tissue, osteoid tissue, and dentin. It is essential for wound healing and facilitates recovery from burns. This vitamin is a strong reducing agent and is reversibly oxidized and reduced in the body, functioning as a redox system in the cell. It is involved in the metabolism of phenylalanine and tyrosine. As a reductant (with oxygen, ferrous iron, and a 2-ketoacid), vitamin C activates enzymes that hydroxylate procollagen proline and lysine to procollagen hydroxyproline and hydroxylysine. In scorbutic animals, elastin becomes increasingly deficient in hydroxyproline. Vitamin C protects folic acid reductase, which converts folic acid to folinic acid, and may help release free folic acid from its conjugates in food. Vitamin C facilitates the absorption of iron.

Severe deficiency results in **scurvy**, an acute or chronic disease characterized by hemorrhagic manifestations and abnormal osteoid and dentin formation.

ETIOLOGY

In adults, primary deficiency is usually due to food idiosyncrasies or improper diet. Deficiencies occur in GI disease, especially when the patient is on an "ulcer diet." Pregnancy, lactation, and thyrotoxicosis increase vitamin C requirements; acute and chronic inflammatory diseases, surgery, and burns can significantly increase requirements. Diarrhea increases fecal loss, and achlorhydria decreases the amount absorbed. Cold or heat stress increases urinary excretion of vitamin C. Heat (eg, sterilization of formulas, cooking) can destroy vitamin C in food.

PATHOLOGY

Formation of intercellular cement substances in connective tissues, bones, and dentin is defective, resulting in weakened capillaries with subsequent hemorrhage and defects in bone and related structures. Hemorrhagic areas are organized avascularly, so that wounds heal poorly and break open easily. Endochondral growth ceases because osteoblasts fail to form osteoid tissue, resulting in bone lesions. Instead, a fibrous union forms between the diaphysis and the epiphysis, and costochondral junctions enlarge. Densely calcified fragments of cartilage are embedded in this fibrous tissue. Small ecchymotic hemorrhages within or along the bone or large subperiosteal hemorrhages due to small fractures just shaftward of the white line complicate these lesions.

Symptoms and Signs

In adults, scurvy remains latent for 3 to 6 mo after the reduction of vitamin C in the diet to < 10 mg/day. Overt scorbutic symptoms are preceded by lassitude,

weakness, irritability, weight loss, and vague myalgias and arthralgias. Multiple splinter hemorrhages may form a crescent near the distal ends of the nail and are more extensive than those in bacterial endocarditis. The gums become swollen, purple, spongy, and friable; they bleed readily in extreme deficiency. Secondary infection, gangrene, and loosening of teeth eventually occur. Such changes affect only the gum around natural teeth or with hidden roots. Old scars break down, new wounds do not heal, and spontaneous hemorrhages may occur in any part of the body, especially as perifollicular petechiae and ecchymoses in the skin of the lower limbs. (In old age, such changes are not necessarily scorbutic.) Bone lesions, except for subperiosteal hemorrhage, do not occur in adults.

Other symptoms and signs of scurvy include bulbar conjunctival hemorrhage, femoral neuropathy from hemorrhage into femoral sheaths, oliguria, edema of the lower extremities, impaired vascular reactivity, and arthritis resembling RA. Bleeding gums are not the most characteristic feature of scurvy. The hyperkeratotic hair follicle with surrounding hyperemia or hemorrhage is almost pathognomonic.

Laboratory Findings and Diagnosis

Plasma ascorbic acid falls from the normal range of 0.6 to 1.4 mg/dL (34 to 79 μmol/L) to < 0.2 mg/dL (< 11 μmol/L), sometimes near zero. Ascorbic acid levels in the WBC-platelet layer of centrifuged blood are more significant; normal levels > 16 μg/108 cells (> 91 nmol/108 cells) are reduced to < 2.0 μg/108 cells (< 11.4 nmol/108 cells). When vitamin C stores are depleted, little appears in the urine after a test dose of vitamin C. A positive capillary fragility test is an almost constant finding, and anemia is common. Bleeding, coagulation, and prothrombin times are normal.

In adults, scurvy must be differentiated from arthritis, hemorrhagic diseases, and gingivitis. Joint symptoms are due to bleeding around or into the joint. The presence of petechial hemorrhages plus blood studies aids in diagnosis.

Prophylaxis and Treatment

Vitamin C 60 mg/day po is fully protective. Most nutritionists believe that huge doses of vitamin C (about 10 g/day) do not decrease the incidence or severity of the common cold (see Respiratory Viral Diseases in Ch. 162) or influence the progress of malignant disease or atherosclerosis. These megadoses acidify the urine; they may cause diarrhea from osmotic effects, predispose to urinary calculi from oxalate, and promote iron overload.

For scurvy in adults, ascorbic acid 100 mg po tid is given for 1 to 2 wk, until signs have disappeared, followed by a nutritious diet supplying one to two times the RDA. The usual maintenance doses can then be given. In scorbutic patients, therapeutic doses of ascorbic acid restore the functions of vitamin C in a few days. The signs and symptoms usually disappear over 1 to 2 wk. Chronic gingivitis with extensive subcutaneous hemorrhage may take somewhat longer.

VITAMIN C DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin C is responsible for a remarkable number of functions in the body. However, the main focus of the prevention and treatment for vitamin C deficiency is on scurvy—a very severe vitamin C deficiency.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone

for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin C, from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

In the Merck Manual statement that high doses of vitamin C can "predispose to urinary calculi from oxalate". According to Dr. Abram Hoffer, there has never been a case of kidney stones caused by high doses of vitamin C. (Hoffer A. "Over The Counter Drugs." Journal of Orthomolecular Medicine. May 2003.)

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Plasma vitamin C, cholesterol and homocysteine are associated with grey matter volume determined by MRI in non-demented old people. Neurosci Lett. May 8;341(3):173-6. 2003.

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We studied 82 non-demented old people and, using MRI, derived measures of grey and white matter and intracranial volumes. Controlling for sex and intracranial volume, we related grey and white matter volumes to plasma concentrations of vitamins C, B(12), folate, homocysteine, cholesterol, triglycerides, high density and low density (LDL) lipoproteins, and to red blood cell folate and glycated haemoglobin concentrations (HbA1(c)). We found that lower grey matter volume was associated with lower plasma vitamin C and higher homocysteine, cholesterol and LDL. Lower blood cell folate was also associated with lower grey matter volume but HbA1(c) was not. These data are consistent with the putative benefits of dietary vitamin C and folate intake and the role of cholesterol in age related neurodegeneration.

PMID: 12697276 [PubMed - indexed for MEDLINE]

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BACKGROUND/AIM: L-Ascorbic acid (AA) is the predominant circulating form of vitamin C found in human blood. It has been hypothesized that surgical stress increases the vitamin C metabolite dehydroascorbic acid (DHAA). Vitamin C is mainly excreted through the kidneys. In this study, the ratio of AA to DHAA excreted in urine was determined in patients who had undergone total hip joint endoprosthesis surgery (n = 12), and the results were compared with data obtained from healthy controls (n = 12). METHODS: All subjects received 1,000 mg sodium ascorbate intravenously three times a day (every 8 h) for 8 days, starting 2 days prior to surgery. Total urine was collected daily while subsequent determinations of AA and DHAA were performed photometrically. RESULTS: Administration of vitamin C led to average daily excretions of the combined products AA + DHAA of 2,343 +/- 438 mg/day (mean value +/- confidence intervals). The initial average ratio DHAA/AA of all 24 probands was 0.064 (6% DHAA; 153 +/- 76 mg/day). One day after surgery, an increase in the DHAA/AA ratio to 0.165 (15% DHAA; 332 +/- 107 mg/day) was measured in the patients. The ratio decreased 2 days after surgery and returned to normal within 5 days. CONCLUSION: Our data indicate that surgery increases the oxidation of AA and urinary excretion of DHAA, as a result of the enhanced formation of free radicals. Copyright 2003 S. Karger AG, Basel.

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RATIONALE: Physiological responses to stress are considered disruptive to health. High-dose ascorbic acid has reduced indices of stress in laboratory animals. METHODS: We conducted a randomized double-blind, placebo-controlled 14-day trial of sustained-release ascorbic acid (60 healthy young adults; 3 x1000 mg/day Cetebe) and placebo (60 healthy young adults) for reduction of blood pressure, cortisol, and subjective response to acute psychological stress (Trier Social Stress Test, TSST, consisting of public speaking and mental arithmetic). Six subjects from each group were excluded. RESULTS: Compared to the placebo group, the ascorbic acid group had less systolic blood pressure (an increase of 23 versus 31 mmHg), diastolic blood pressure, and subjective stress responses to the TSST; and also had faster salivary cortisol recovery (but not smaller overall cortisol response). Cortisol response to 1 microg ACTH, and reported side-effects during the trial did not differ between groups. Plasma ascorbic acid level at the end of the trial but not pre-trial was associated with reduced stress reactivity of systolic blood pressure, diastolic blood pressure, and subjective stress, and with greater salivary cortisol recovery. CONCLUSIONS: Treatment with high-dose sustained-release ascorbic acid palliates blood pressure, cortisol, and subjective response to acute psychological stress. These effects are not attributable to modification of adrenal responsiveness.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 11862365 [PubMed - indexed for MEDLINE]

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Alzheimer's disease is a progressive neurodegenerative disorder characterized by a gradual decline in memory. The occurrence of Alzheimer's disease is commonplace among the Asian population, particularly among senior citizens. The present study was undertaken to assess the potential of ascorbic acid as a memory-enhancer. Swiss mice of either sex were employed in the present investigation. Elevated plus-maze and passive-avoidance apparatus served as the exteroceptive behavioral models, and diazepam-, scopolamine-, and aging-induced amnesia served as the interoceptive behavioral models. Ascorbic acid (60, 120 mg/kg) injected for 3 and 8 consecutive days improved learning and memory of aged mice as indicated by decreased transfer-latency and increased step-down latency. Furthermore, ascorbic acid provided protection to the young animals from scopolamine- and diazepam-induced impairment of memory. Ascorbic acid was found to be more potent than piracetam as reflected by the smaller dose, more pronounced effect, and quicker onset of action. Ascorbic acid has shown promise as a powerful memory-improving agent particularly effective in aged animals. Hence, ascorbic acid might prove to be a useful memory-restorative agent in the treatment of dementia seen in elderly individuals. The underlying mechanism of action of ascorbic acid may be attributed to its antioxidant property.

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VITAMIN D (CHOLECALCIFEROL)

Vitamin D: Studies have shown an association between the lack of vitamin D deficiency or imbalance and anxiety[1], depression[2,3], and premenstrual syndrome[4,5].

The following description of Vitamin D is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

VITAMIN D DEFICIENCY AND DEPENDENCY

This fat-soluble vitamin occurs mainly in two forms: ergocalciferol (activated ergosterol, vitamin D2), found in irradiated yeast; and cholecalciferol (activated 7-dehydrocholesterol, vitamin D3), formed in human skin by exposure to sunlight (ultraviolet radiation) and found chiefly in fish liver oils and egg yolks. Milk is fortified with both forms. Synthesis in the skin is normally the major source. One microgram of vitamin D equals 40 IU.

Vitamin D is a prohormone with several active metabolites that act as hormones. In the skin, previtamin D3 is synthesized photochemically from 7-dehydrocholesterol and is slowly isomerized to vitamin D3, which is removed by vitamin D-binding protein. In the liver, vitamin D3 is converted to 25(OH)D3, the major circulating form. It passes through the enterohepatic circulation and is reabsorbed from the gut. Principally in the kidneys, it is further hydroxylated to the much more metabolically active form, 1,25(OH)2D3 (1,25-dihydroxycholecalciferol, calcitriol, vitamin D hormone). The main function of vitamin D hormone is to increase calcium absorption from the intestine and promote normal bone formation and mineralization. These functions are mediated by a vitamin D receptor that is a transcription factor, which is instrumental in turning on a panoply of genes that express the biologic activity of vitamin D hormone. The critical 1-hydroxylation of 25(OH)D3 is strongly stimulated by parathyroid hormone (PTH) and, independently of PTH, by hypophosphatemia. The actions of vitamin D and its metabolites are summarized in Table 3-1.

Vitamin D is used to treat renal osteodystrophy caused by chronic renal failure (see Ch. 222).

Metabolic bone disease resulting from vitamin D deficiency is called **rickets** in children and **osteomalacia** in adults. These diseases result from common pathogenetic factors but differ in their clinical and pathologic expression because of the differences between growing and mature bones.

ETIOLOGY

Inadequate exposure to sunlight and low dietary intake are usually necessary for development of clinical vitamin D deficiency. Rickets is not uncommon in the tropics because infants are swaddled and women and children are confined to the home. Nutritional rickets is rare in the USA but is not uncommon among Indian immigrants to Britain, where lack of sunlight, chelation of calcium by consumption of their traditional cereal diet, and low intake of milk are probably responsible. Rarely, very low intake of calcium or phosphorus may be the cause.

Vitamin D deficiency may also be caused by defects in the production of 25(OH)D3 or the action of 1,25(OH)2D3 (see Table 3-2). The deficiency may occur in hypoparathyroidism (see Hypocalcemia under Disorders of Calcium Metabolism in

Ch. 12); in hereditary diseases, such as familial hypophosphatemic (vitamin D-resistant) rickets, an X-linked dominant disorder (see Anomalies in Kidney Transport in Ch. 261); and in various other diseases. Some diseases interfere with the absorption of vitamin D or with the formation of its active metabolites. Deficiency of vitamin D metabolites results in vitamin D-resistant states.

Rickets and osteomalacia may occur when the supply of vitamin D is inadequate, its metabolism is abnormal, or tissues are resistant to its action. Categorizing rickets and osteomalacia by etiology is important in relation to the manifestations of disease and to effective treatment.

PATHOLOGY

In children, changes include defective calcification of growing bone and hypertrophy of the epiphyseal cartilages. Epiphyseal cartilage cells cease to degenerate normally, but new cartilage continues to form, so that the epiphyseal cartilage becomes irregularly increased in width. Calcification then stops, and osteoid material accumulates around the capillaries of the diaphysis. The cancellous bone of the diaphysis and cortical bone may be resorbed in chronic deficiency.

Adequate treatment with vitamin D permits calcium and phosphate deposition through degeneration of the cartilage cells within 24 h and penetration by a vascular network within 48 h. Osteoid material at the diaphysis ceases to form, and normal endochondral production of new bone is resumed.

In adults, the changes are similar but are not confined to the ends of the long bones.

Symptoms and Signs

Maternal osteomalacia can lead to metaphyseal lesions and tetany in the newborn. Young infants are restless and sleep poorly. They have reduced mineralization of the skull (craniotabes), away from the sutures. In older infants, sitting and crawling are delayed as is fontanelle closure, and there is bossing of the skull and costochondral beading (rachitic rosary). In children aged 1 to 4 yr, epiphyseal cartilages at the lower ends of the radius, ulna, tibia, and fibula enlarge; kyphoscoliosis develops, and walking is delayed. In older children and adolescents, walking is painful, and in extreme cases, such deformities as bowlegs and knock-knees develop.

Rachitic tetany is caused by hypocalcemia and may accompany infantile or adult vitamin D deficiency. The clinical findings are discussed in Hypocalcemia under Disorders of Calcium Metabolism in Ch. 12.

Bone changes, visible on x-rays, precede clinical signs, becoming evident in the 3rd or 4th mo of life—even at birth if the mother is vitamin D deficient. Bone changes in rickets are most evident at the lower ends of the radius and ulna. The diaphyseal ends lose their sharp, clear outline; are cup-shaped; and show a spotty or fringy rarefaction. Later, the distance between the ends of the radius and ulna and the metacarpal bones appears increased because the true ends are noncalcified and invisible. The shadows cast by the shaft decrease in density, and the network formed by laminae becomes coarse. Characteristic deformities result from the bones bending at the cartilage-shaft junction because the shaft is weak. As healing begins, a thin white line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds. Later, calcium salts are deposited beneath the periosteum, the shaft casts a denser shadow, and the lamellae disappear.

In adults, demineralization (osteomalacia) occurs, particularly in the spine, pelvis, and lower extremities; the fibrous lamellae become visible on x-rays, and incomplete ribbonlike areas of demineralization (pseudofractures, Looser's lines, Milkman's syndrome) appear in the cortex. As the bones soften, weight may cause bowing of the long bones, vertical shortening of the vertebrae, and flattening of the pelvic bones, which narrows the pelvic outlet.

Laboratory Findings

25(OH)D3 and other vitamin D metabolites may be measured in plasma. In healthy persons, levels are 25 to 40 ng/mL (62.4 to 99.8 nmol/L) for 25(OH)D3 and 20 to 45 pg/mL (48 to 108 pmol/L) for 1,25(OH)2D3. In nutritional rickets and osteomalacia, 25(OH)D3 levels are very low, and 1,25(OH)2D3 is undetectable. A low serum phosphorus (normal: 3.0 to 4.5 mg/dL [0.97 to 1.45 mmol/L]) and a high serum alkaline phosphatase are characteristic. Serum calcium is low or normal, depending on the effectiveness of secondary hyperparathyroidism in restoring serum calcium to normal. Serum PTH is elevated, and urinary calcium is low in all forms of the disease except those associated with acidosis. In hereditary vitamin D-dependent rickets, laboratory findings vary (see below).

Diagnosis

A history of inadequate vitamin D intake suggests rickets and helps distinguish it from infantile scurvy and other conditions. It can be distinguished from congenital syphilis (identified by serologic and other tests) and from chondrodystrophy (identified by a large head, short extremities, thick bones, and normal serum calcium, phosphorus, and phosphatase levels).

Osteogenesis imperfecta, cretinism, congenital dislocation of the hip, hydrocephalus, and poliomyelitis should be readily distinguishable. Manifest tetany in infantile rickets must be differentiated from convulsions due to other causes. Rickets refractory to vitamin D may be caused by severe renal damage, or it may occur in renal tubular acidosis, X-linked familial hypophosphatemia, or Fanconi's syndrome (see Anomalies in Kidney Transport in Ch. 261).

Osteomalacia must be differentiated from other causes of widespread bone decalcification (eg, hyperparathyroidism, senile or postmenopausal osteoporosis, the osteoporosis of hyperthyroidism, Cushing's syndrome, multiple myeloma, and atrophy of disuse). Changes in serum calcium, phosphate, alkaline phosphatase, and 25(OH)D3 levels, together with x-ray findings, confirm the diagnosis.

PROPHYLAXIS

Health education, including dietary advice, should be given to susceptible communities. Human breast milk is deficient in vitamin D, containing an average of only 1.0 μg/L (40 IU/L), mostly as 25(OH)D3, whereas fortified cow's milk contains 10 μg/L (400 IU/L). Breastfed infants should be given a supplement of vitamin D 7.5 μg (300 IU)/day from birth to 6 mo, at which time a more diversified diet is available. Vitamin D fortification of unleavened chapati flour (125 μg/kg) has been effective among Indian immigrants in Britain. Among adolescents in the Far East, a single IM dose of 2.5 mg (100,000 IU) ergocalciferol given in the fall has produced a substantial increase in plasma 25(OH)D3 lasting until spring.

Treatment

With adequate calcium and phosphorus intake, osteomalacia and uncomplicated rickets can be cured by giving vitamin D 40 μg (1600 IU)/day. Serum 25(OH)D3 and 1,25(OH)2D3 begin to rise within 1 or 2 days. Serum phosphorus rises in about 10 days. The response of a rachitic child to vitamin D treatment is shown in Fig. 3-1. During the 3rd wk, signs of calcium and phosphorus deposition in the osseous tissues can be seen on x-rays. After about 1 mo of therapy, the dose can be reduced gradually to the usual maintenance level of 10 μg (400 IU)/day. If tetany is present, vitamin D should be supplemented with IV calcium salts during the first week (see Hypocalcemia under Disorders of Calcium Metabolism in Ch. 12).

VITAMIN D DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin D is responsible for a number of functions in the body. However, the main focus of the prevention and treatment for vitamin D deficiency is on rickets—a very severe vitamin D deficiency.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin D from lack of essential nutrients found in fresh foods, which leads to a host of health problems. The current practice of covering children's body's with sunscreen, further prevents their access to vitamin D from the sun.

VITAMIN D TOXICITY

Vitamin D 1000 μg (40,000 IU)/day produces toxicity within 1 to 4 mo in infants, and as little as 75 μg (3000 IU)/day can produce toxicity over years. Toxic effects have occurred in adults receiving 2500 μg (100,000 IU)/day for several months. Elevated serum calcium levels of 12 to 16 mg/dL (3 to 4 mmol/L) are a constant finding when toxic symptoms occur; normal levels are 8.5 to 10.5 mg/dL (2.12 to 2.62 mmol/L). *Serum calcium should be measured frequently (weekly at first, then monthly) in all patients receiving large doses of vitamin D.*

The first symptoms are anorexia, nausea, and vomiting, followed by polyuria, polydipsia, weakness, nervousness, and pruritus. Renal function is impaired, as evidenced by low sp gr urine, proteinuria, casts, and azotemia. Metastatic calcifications may occur, particularly in the kidneys. Plasma 25(OH)D3 levels are elevated as much as fifteenfold in vitamin D toxicity, whereas 1,25(OH)2D3 levels are usually within the normal range.

A history of excessive vitamin D intake is critical for differentiating this condition from all other hypercalcemic states. Vitamin D toxicity occurs commonly during the treatment of hypoparathyroidism (see Hypocalcemia under Disorders of Calcium Metabolism in Ch. 12) and with the misguided use of megavitamins. In Great Britain, so-called **hypercalcemia in infancy with failure to thrive** has occurred with a daily vitamin D intake of 50 to 75 μg (2000 to 3000 IU). **Williams syndrome** consists of transient hypercalcemia in infancy with the triad of supravalvular aortic stenosis, mental retardation, and elfin facies. Plasma levels of 1,25(OH)2D3 during the hypercalcemic phase are 8 to 10 times normal. Most cases

are due to an unidentified defect in vitamin D metabolism rather than to excessive intake.

1,25(OH)2D3 is 100 times more potent than vitamin D3. When it is used to treat various disorders, possible toxic effects of long-term therapy must be watched for.

Treatment consists of discontinuing the vitamin, providing a low-calcium diet, keeping the urine acidic, and giving corticosteroids. Kidney damage or metastatic calcification, if present, may be irreversible. Diuretics and forced fluids are not helpful.

VITAMIN D REFERENCES

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VITAMIN E (D-ALPHA TOCOPHERYL SUCCINATE)

Vitamin E: Research has demonstrated a link between vitamin E deficiency or imbalance and anxiety[1], depression[2], premenstrual syndrome[3,4,5,6,7], schizophrenia[8], Alzheimer's[9,10], age-related disorders[11], oxidative stress[12], and endurance training[13].

The following description of Vitamin E is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

VITAMIN E DEFICIENCY

Vitamin E (tocopherol) is a generic term for compounds that have a 6-chromanol ring, an isoprenoid side chain, and the biologic activity of -tocopherol. The vitamin E group contains -, -, -, and -tocopherols, which vary in the extent to which the chromanol ring is methylated. d--Tocopherol is the only naturally occurring stereoisomer and the most potent in biologic assays (1.49 IU/mg); the totally synthetic dl--tocopherol is completely racemic and has less biologic activity (1.1 IU/mg) than d--tocopherol. The international standard is dl--tocopherol acetate (1.0 IU/mg). In general, tocopherols act as antioxidants to prevent lipid peroxidation of polyunsaturated fatty acids in cellular membranes. The antioxidant activity of -tocopherol is similar to that of glutathione peroxidase, which contains selenium (see Selenium in Ch. 4). In humans, plasma tocopherol levels vary with the total plasma lipid levels, which affect the partition between plasma and adipose tissue, the main storage depot for tocopherols. Normally, the plasma -tocopherol level is 5 to 10 μg/mL (11.6 to 23.2 μmol/L).

The diseases caused by vitamin E deficiency vary widely according to species. The deficiency may cause disorders of reproduction; abnormalities of muscle, liver, bone marrow, and brain function; hemolysis of RBCs; defective embryogenesis; and exudative diathesis, a disorder of capillary permeability. Skeletal muscle dystrophy may occur and, in certain species, is accompanied by cardiomyopathy.

In humans, the main manifestations of vitamin E deficiency are (1) mild hemolytic anemia associated with increased erythrocyte hemolysis and (2) spinocerebellar disease (see under Cerebellar and Spinocerebellar Disorders in Ch. 179), which occurs mainly in children who have fat malabsorption due to abetalipoproteinemia, chronic cholestatic hepatobiliary disease, celiac disease, or a genetic abnormality in vitamin E metabolism.

Retinopathy of prematurity, also called retrolental fibroplasia (see Retinopathy of Prematurity in Ch. 260), may improve with vitamin E therapy, as may some cases of intraventricular and subependymal hemorrhage in the newborn.

ETIOLOGY

Infants are born in a state of relative vitamin E deficiency, with plasma -tocopherol levels below 5 μg/mL (11.6 μmol/L). The smaller and more premature the infant, the greater the degree of deficiency. Vitamin E deficiency in premature infants persists during the first few weeks of life and can be attributed to limited placental transfer of vitamin E, low tissue levels at birth, relative dietary deficiency in infancy, intestinal malabsorption, and rapid growth. As the digestive system matures, vitamin E absorption improves, and blood vitamin E levels rise.

In children and adults, malabsorption generally underlies vitamin E deficiency. Genetic abnormality in the transport of vitamin E can also play a role.

Symptoms and Signs

Hemolytic anemia in premature infants may be a manifestation of vitamin E deficiency. Such an infant has hemoglobin levels ranging from 7 to 9 g/dL, low plasma vitamin E levels, reticulocytosis, and hyperbilirubinemia.

Children with chronic cholestatic hepatobiliary disease or cystic fibrosis manifest the neurologic syndrome of vitamin E deficiency. Its signs are spinocerebellar ataxia with loss of deep tendon reflexes, truncal and limb ataxia, loss of vibration and position sense, ophthalmoplegia, muscle weakness, ptosis, and dysarthria. In adults with malabsorption, spinocerebellar ataxia due to vitamin E deficiency is extremely rare, no doubt because adults have large vitamin E stores in adipose tissue. The clinical features of vitamin E deficiency are listed in Table 3-3.

Laboratory Findings and Diagnosis

Premature infants deficient in vitamin E have muscular weakness, creatinuria, and ceroid pigmentation with necrosis in muscle biopsies. Increased peroxide hemolysis is also observed. Plasma tocopherol levels are < 4 μg/mL (< 9.28 μmol/L). **In adults**, vitamin E deficiency should be considered when the plasma tocopherol level is < 5 μg/mL (< 11.6 μmol/L) with enhanced susceptibility of RBCs to hydrogen peroxide. If hyperlipemia is present, the -tocopherol level is elevated, and deficiency is diagnosed when the tocopherol level is < 0.7 mg/g (< 1.6 μmol/g) of plasma fat, which corresponds to < 5 μg/mL (< 11.6 μmol/L) in a normolipemic person.

Treatment

The preventive dose of -tocopherol is 0.5 mg/kg for full-term infants and 5 to 10 mg/kg for premature infants.

For malabsorption causing overt deficiency, 15 to 25 mg/kg/day of -tocopherol should be given po as water-miscible d—tocopheryl acetate (1 mg = 1.4 IU).

Much larger doses (up to 100 mg/kg/day po in divided doses) are required to treat neuropathy early or to overcome the defect of absorption and transport in abetalipoproteinemia. Such treatment has alleviated symptoms in young patients and arrested the neuropathy in older patients.

In the genetic form of vitamin E deficiency without fat malabsorption, megadoses of -tocopherol (100 to 200 IU/day) ameliorate the deficiency and prevent neurologic sequelae.

VITAMIN E DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "Infants are born in a state of relative vitamin E deficiency." How they make up for that deficiency is based on adequate intake from the diet. In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." In the case of vitamin E, we maintain that children are born with a vitamin E deficiency and unless their mothers eat vitamin E rich foods and breast feed and then feed their

children these foods: mustard greens, chard, sunflower seeds, and turnip greens and wheat germ, they will not achieve vitamin E sufficiency.

The Merck Manual citation states that "In general, tocopherols act as antioxidants to prevent lipid peroxidation of polyunsaturated fatty acids in cellular membranes." And that "The diseases caused by vitamin E deficiency vary widely according to species. The deficiency may cause disorders of reproduction; abnormalities of muscle, liver, bone marrow, and brain function; hemolysis of RBCs; defective embryogenesis; and exudative diathesis, a disorder of capillary permeability. Skeletal muscle dystrophy may occur and, in certain species, is accompanied by cardiomyopathy." However, they minimize the status of vitamin E deficiency in humans by saying that "In humans, the main manifestations of vitamin E deficiency are (1) mild hemolytic anemia associated with increased erythrocyte hemolysis and (2) spinocerebellar disease."

This statement about vitamin E deficiency in humans can only be said because, according to the Merck Manual, there has not been enough research to prove the brain, reproductive, heart effects and stress effects of vitamin E deficiency. Until those studies are done we really do not know the extent of vitamin E deficiency in the population or the symptoms that may result.

VITAMIN E TOXICITY

Adults have taken relatively large amounts of vitamin E (400 to 800 mg/day of d--tocopherol) for months to years without any apparent harm. Occasionally, muscle weakness, fatigue, nausea, and diarrhea have occurred in persons taking 800 to 3200 mg/day. The most significant toxic effect of vitamin E at > 1000 mg/day is antagonism to vitamin K action and enhancement of the effect of oral coumarin anticoagulants, which may result in overt hemorrhage.

VITAMIN E REFERENCES

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8. Arvindakshan M, et al. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. Schizophr. Res. 62(3): 195-204; 2003.

9. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC; Cache County Study Group. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol. Jan;61(1):82-8. 2004

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BACKGROUND: Antioxidants may protect the aging brain against oxidative damage associated with pathological changes of Alzheimer disease (AD). OBJECTIVE: To examine the relationship between antioxidant supplement use and risk of AD. DESIGN: Cross-sectional and prospective study of dementia. Elderly (65 years or older) county residents were assessed in 1995 to 1997 for prevalent dementia and AD, and again in 1998 to 2000 for incident illness. Supplement use was ascertained at the first contact. SETTING: Cache County, Utah. PARTICIPANTS: Among 4740 respondents (93%) with data sufficient to determine cognitive status at the initial assessment, we identified 200 prevalent cases of AD. Among 3227 survivors at risk, we identified 104 incident AD cases at follow-up. MAIN OUTCOME MEASURE: Diagnosis of AD by means of multistage assessment procedures. RESULTS: Analyses of prevalent and incident AD yielded similar results. Use of vitamin E and C (ascorbic acid) supplements in combination was associated with reduced AD prevalence (adjusted odds ratio, 0.22; 95% confidence interval, 0.05-0.60) and incidence (adjusted hazard ratio, 0.36; 95% confidence interval, 0.09-0.99). A trend toward lower AD risk was also evident in users of vitamin E and multivitamins containing vitamin C, but we saw no evidence of a protective effect with use of vitamin E or vitamin C supplements alone, with multivitamins alone, or with vitamin B-complex supplements. CONCLUSIONS: Use of vitamin E and vitamin C supplements in combination is associated with reduced prevalence and incidence of AD. Antioxidant supplements merit further study as agents for the primary prevention of AD.

10. Martin A. Antioxidant vitamins E and C and risk of Alzheimer's disease. Nutr Rev. Feb;61(2):69-73. 2003.

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Age-related neurodegenerative disorders are increasing rapidly. Alzheimer's disease is the most common cause of dementia associated with aging. A recent study has examined the role of vitamins E and C in a prospective epidemiologic cohort study and suggested that they might protect against Alzheimer's disease.

Publication Types:
* Review
* Review, Tutorial

11. Polidori MC. Antioxidant micronutrients in the prevention of age-related diseases. J Postgrad Med. Jul-Sep;49(3):229-35. 2003.

Institut fur Biochemie und Molekularbiologie I, Heinrich-Heine-Universitat Dusseldorf, Universitatsstr. 1, Geb. 22.03, D-40225 Dusseldorf, Germany. polidori@uni-duesseldorf.de

The role and functions of antioxidant micronutrients such as ascorbate (vitamin C), a-tocopherol (vitamin E) and carotenoids that are provided through the diet in aging and in the prevention of age-related diseases are discussed in the present work. In general, a healthy lifestyle involving regular exercise and avoidance of tobacco or alcohol abuse are the key to the prevention of several age-related diseases including cardiovascular diseases, dementia and cancer. A balanced and regular nutrition with at least five portions of fruit and vegetables per day is a critical constituent of such a healthy lifestyle.

Publication Types:
* Review
* Review, Tutorial

PMID: 14597786 [PubMed - indexed for MEDLINE]

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Vitamin E and carotenoids are known to act as antioxidants both in vitro and in vivo. In this review we present a series of studies in healthy subjects and in patients who exhibit either acute or chronic oxidative stress. In the EU-Commission funded VITAGE project we investigated the status and effects of vitamin E and carotenoids on oxidative stress in 300 healthy volunteers. Depletion studies limiting dietary vitamin E or carotenoid intake to approximately 25% of the dietary reference intakes and subsequent repletion by supplementation with either large doses of vitamin E or intermediate doses of carotenoids showed significant changes in ex vivo LDL oxidizability, total plasma peroxide concentrations and urinary 8-oxo-7,8-dihydro-2(')-deoxyguanosine excretion. Patients on chronic hemodialysis present with oxidative stress in the presence of normal vitamin E but impaired vitamin C status and, due to anemia, need to be treated with parenteral iron. We studied the effects of a single oral dose of vitamin E taken 6 h prior to intravenous infusion of 100 mg iron, which exceeded the iron-binding capacity of transferrin. Vitamin E significantly reduced and in combination with a single dose of vitamin C completely abrogated acute oxidative stress induced by the iron load. Patients with cystic fibrosis are exposed to chronic oxidative stress due to an overproduction of reactive oxygen species as a result of neutrophil-dominated lung inflammation and impaired antioxidant status. Biochemical vitamin E and carotenoid deficiencies could be fully corrected even in the presence of fat malabsorption using intermediate doses of either RRR alpha-tocopherol or all-rac alpha-tocopheryl acetate and water-miscible all-trans beta-carotene. Long-term supplementation reduced ex vivo LDL oxidizability, in vivo lipid peroxidation and lung inflammation.

Publication Types:
* Review
* Review, Tutorial

PMID: 14585310 [PubMed - indexed for MEDLINE]

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Comment in:
* Int J Sport Nutr. 1994 Sep;4(3):203-4.
* Int J Sport Nutr. 1995 Jun;5(2):165-7.

Institute of Forensic Medicine, University Hospital, Freiburg, Germany.

This study was undertaken to evaluate the effects of 5 months of alpha-tocopherol supplementation on physical performance during aerobic exercise training in 30 top-class cyclists. Antioxidative effects of supplementation were also studied. Plasma alpha-tocopherol concentration increased significantly in the vitamin E-supplemented group, whereas the placebo group showed a trend toward decrease. Physical performance did not improve in the alpha-tocopherol-supplemented group compared to the placebo group. Heart rates were also not significantly different. Lactate concentrations at the aerobic threshold and the anaerobic threshold were identical. Thus, there was no performance improvement in the alpha-tocopherol-supplemented group. However there was a significant reduction in CK in serum of the E-supplemented group. A trend toward decrease in GOT, GPT, and LDH was observed with alpha-tocopherol supplementation. Moreover, significantly reduced malondialdehyde serum levels were measured in the E-supplemented group. The findings indicate a protective effect of alpha-tocopherol supplementation against oxidative stress induced by strenuous exercise.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 7987360 [PubMed - indexed for MEDLINE]

VITAMIN B1 (THIAMINE MONONITRATE)

Research has demonstrated a link between vitamin B1 deficiency or imbalance and neurodegeneration[1], neuron damage[2], neurotransmitters and DNA synthesis[3], infant depletion[4], and memory[5].

The following description of Vitamin B1 is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

THIAMINE DEFICIENCY AND DEPENDENCY

The coenzyme thiamine pyrophosphate, the active form of thiamine (vitamin B1), participates in carbohydrate metabolism through decarboxylation of -keto acids. Thiamine also acts as coenzyme to the apoenzyme transketolase in the pentose monophosphate pathway for glucose. Deficiency causes **beriberi** with peripheral neurologic, cerebral, cardiovascular, and GI manifestations.

ETIOLOGY

Primary thiamine deficiency is caused by inadequate intake of thiamine, particularly in people subsisting on highly polished rice. Milling removes the husk, which contains most of the thiamine, but boiling before husking disperses the vitamin throughout the grain, thus preventing its loss.

Secondary thiamine deficiency is caused by increased requirement, as in hyperthyroidism, pregnancy, lactation, and fever; impaired absorption, as in prolonged diarrheas; and impaired utilization, as in severe liver disease. A combination of decreased intake, impaired absorption and utilization, increased requirements, and possibly an apoenzyme defect occurs in alcoholism. Frequent, long-term, or highly concentrated dextrose infusions, coupled with low thiamine intake, may precipitate thiamine deficiency.

PATHOLOGY

The most advanced neural changes occur in the peripheral nerves, particularly of the legs. The distal segments are characteristically affected earliest and most severely. Degeneration of the medullary sheath can occur in all tracts of the spinal cord, especially in the posterior columns and in the anterior and posterior nerve roots. Changes also occur in the anterior horn and posterior ganglion cells. Lesions of hemorrhagic polioencephalitis occur in the brain when deficiency is severe.

The heart is dilated and enlarged; muscle fibers are swollen, fragmented, and vacuolized, with interstitial spaces dilated by fluid. Vasodilation occurs and can result in some edema before frank high-output heart failure occurs.

Symptoms and Signs

Early deficiency produces fatigue, irritation, poor memory, sleep disturbances, precordial pain, anorexia, abdominal discomfort, and constipation.

The syndrome of **peripheral neurologic changes** due to thiamine deficiency is called **dry beriberi**. These changes are bilateral and symmetric, involving predominantly the lower extremities, and begin with paresthesias of the toes, burning of the feet (particularly severe at night), muscle cramps in the calves, and pains in the legs. Calf muscle tenderness, difficulty in rising from a squatting position, a decrease in the vibratory sensation in the toes, and plantar dysesthesia

are early signs. A diagnosis of mild peripheral neuropathy can be made when ankle jerks are absent. Continued deficiency causes loss of knee jerk, loss of vibratory and position sensation in the toes, atrophy of the calf and thigh muscles, and finally footdrop and toedrop. The arms may be affected after leg signs are well established.

Cerebral beriberi (**Wernicke-Korsakoff syndrome**) results from severe acute deficiency superimposed on chronic deficiency (see Amnesias in Ch. 169). Mental confusion, aphonia, and confabulation constitute the early stage, called **Korsakoff's syndrome**. Cerebral blood flow is markedly reduced and vascular resistance increased. **Wernicke's encephalopathy** consists of nystagmus, total ophthalmoplegia, coma, and, if untreated, death.

Cardiovascular (wet) beriberi (Shoshin beriberi) occurs in thiamine deficiency when myocardial disease is prominent. This causes a high cardiac output with vasodilation and warm extremities. Before heart failure occurs, tachycardia, a wide pulse pressure, sweating, warm skin, and lactic acidosis develop. With heart failure, orthopnea and pulmonary and peripheral edema occur; vasodilation continues, sometimes resulting in shock.

Infantile beriberi occurs in infants (usually between the 2nd and 4th mo of life) who are breastfed by thiamine-deficient mothers. Heart failure, aphonia, and absent deep tendon reflexes are characteristic.

Laboratory Findings

Elevated blood pyruvate and lactate and diminished urinary thiamine excretion (< 50 μg/day) are consistent with the diagnosis of beriberi. Erythrocyte transketolase activity diminishes before and increases after administration of thiamine pyrophosphate (TPP effect) and is a sensitive indicator of tissue stores. Variations in apoenzyme levels in some cases may complicate interpretation of the test.

Diagnosis

A form of polyneuropathy, which does not respond to thiamine, occurs in uncontrolled or long-standing diabetes mellitus and in alcoholism and is clinically similar to that of thiamine deficiency. Other forms of bilateral symmetric polyneuropathy beginning in the legs are uncommon. Single-nerve neuritides (mononeuropathies), such as sciatica, and polyneuropathies beginning elsewhere in the body are unlikely to be due to thiamine deficiency.

Diagnosis of cardiovascular beriberi is difficult when thiamine deficiency is complicated by hypertensive or degenerative heart disease, viral myocardiopathy, or rheumatic fever. A therapeutic trial of thiamine can be helpful in making the diagnosis.

Treatment

For mild polyneuropathy, 10 to 20 mg/day of thiamine is given in divided doses for 2 wk, followed by a nutritious diet. The dosage is 20 to 30 mg/day for moderate or advanced neuropathy and should be continued for several weeks after the symptoms disappear. The edema and congestion of Shoshin beriberi respond in a few hours to 100 mg/day of thiamine IV, which should be continued for several days, plus bed rest. Heart failure due to beriberi responds poorly to digitalis or diuretics.

For Wernicke-Korsakoff syndrome, thiamine 50 to 100 mg IM or IV bid must usually be given for several days, followed by 10 to 20 mg daily until a therapeutic

response is obtained. Anaphylactic reactions to IV thiamine unrelated to the dose are rare.

Thiamine deficiency is often associated with other B-complex deficiencies, and multiple water-soluble vitamin therapy at 5 to 10 times the RDA is usually advisable for several weeks. This regimen should be followed indefinitely by a nutritious diet supplying one to two times the RDA.

Magnesium, a cofactor for transketolase, should be given as magnesium sulfate (1 to 2 mL IM of a 50% solution) with thiamine to correct thiamine resistance and the frequently accompanying hypomagnesemia. Hyponatremia (see Ch. 12) should be corrected *slowly*, because rapid correction may cause central pontine myelinolysis. Recovery from neurologic deficits is often incomplete in beriberi. In cerebral beriberi, central pontine myelinolysis may be residual.

VITAMIN B1 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "The coenzyme thiamine pyrophosphate, the active form of thiamine (vitamin B1), participates in carbohydrate metabolism" and "glucose" metabolism. They further state that "Deficiency causes **beriberi** with peripheral neurologic, cerebral, cardiovascular, and GI manifestations."

The question on the minds of nutritional researchers is whether mild B1 deficiency that is not severe enough to cause beriberi can be one of the factors in the rise of obesity, diabetes, metabolic syndrome, and syndrome X since vitamin B1 is necessary for carbohydrate and glucose metabolism. The Merck Manual also states that "Early deficiency produces fatigue, irritation, poor memory, sleep disturbances, precordial pain, anorexia, abdominal discomfort, and constipation." These symptoms are very common in the general patient population and indications are that treatment with vitamin B1, along with the other B vitamins can alleviate the above symptoms.

Even though Vitamin B1 is an essential coenzyme in a number of important functions in the body, the main focus of the Merck Manual citation is on vitamin B1 deficiency causing beriberi—a very severe vitamin B1 deficiency condition.

According to Singleton and Martin, 2001, "A state of severe depletion is seen in patients on a strict thiamine-deficient diet in 18 days." And thiamine is "important in the biosynthesis of a number of cell constituents, including neurotransmitters, and for the production of reducing equivalents used in oxidant stress defenses and in biosyntheses and for synthesis of pentoses used as nucleic acid precursors (for DNA synthesis)." In Baker, et.al., 2000, "We noted that subclinical thiamin hypovitaminemia is prominent during pregnancy despite vitamin supplementation. Perhaps increased thiamin supplementation during pregnancy seems warranted to avoid metabolic stress in mother and fetus due to thiamin hypovitaminemia."

From the above studies we learn that vitamin B1 deficiency can occur in 18 days and that despite current levels of supplementation for pregnany women, there still exists vitamin B1 deficiency.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy

adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B1 from lack of essential nutrients found in whole foods, which leads to a host of health problems.

VITAMIN B1 REFERENCES

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Thiamine-dependent processes are diminished in brains of patients with several neurodegenerative diseases. The decline in thiamine-dependent enzymes can be readily linked to the symptoms and pathology of the disorders. Why the reductions in thiamine linked processes occur is an important experimental and clinical question. Oxidative stress (i.e. abnormal metabolism of free radicals) accompanies neurodegeneration and causes abnormalities in thiamine-dependent processes. The vulnerability of thiamine homeostasis to oxidative stress may explain deficits in thiamine homeostasis in numerous neurological disorders. The interactions of thiamine with oxidative processes may be part of a spiral of events that lead to neurodegeneration, because reductions in thiamine and thiamine-dependent processes promote neurodegeneration and cause oxidative stress. The reversal of the effects of thiamine deficiency by antioxidants, and amelioration of other forms of oxidative stress by thiamine, suggest that thiamine may act as a site-directed antioxidant. The data indicate that the interactions of thiamine-dependent processes with oxidative stress are critical in neurodegenerative processes.

Publication Types:
* Review
* Review, Academic

PMID: 11850106 [PubMed - indexed for MEDLINE]

2. Park LC, Zhang H, Gibson GE. Co-culture with astrocytes or microglia protects metabolically impaired neurons. Mech Ageing Dev. 2001 Dec;123(1):21-7.

Department of Neurology and Neuroscience, Weill Medical College of Cornell University at Burke Medical Research Institute, 785 Mamaroneck Avenue, White Plains, NY 10605, USA.

Thiamine deficiency (TD) is a model of chronic impairment of oxidative metabolism that leads to neurodegeneration. TD induces oxidative stress and death in neurons, but does not kill astrocytes, microglia or brain endothelial cells. TD primary hippocampal neurons were either cultured alone, or co-cultured with primary astrocytes or microglia. After 7 days of TD, 50% of the neurons died, and the processes of many of the surviving neurons were severely truncated. When TD neurons were co-cultured with astrocytes or microglia, neurons did not die nor show decreased neurite outgrowth. Thus, neuronal-glial interactions are critical for maintaining neuronal homeostasis during chronic metabolic impairment.

PMID: 11640948 [PubMed - indexed for MEDLINE]

3. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. Curr Mol Med. 2001 May;1(2):197-207.

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Thiamine is required for all tissues and is found in high concentrations in skeletal muscle, heart, liver, kidneys and brain. A state of severe depletion is seen in patients on a strict thiamine-deficient diet in 18 days, but the most common cause of thiamine deficiency in affluent countries is alcoholism. Thiamine diphosphate is the active form of thiamine, and it serves as a cofactor for several enzymes involved primarily in carbohydrate catabolism. The enzymes are important in the biosynthesis of a number of cell constituents, including neurotransmitters, and for the production of reducing equivalents used in oxidant stress defenses and in biosyntheses and for synthesis of pentoses used as nucleic acid precursors. Because of the latter fact, thiamine utilization is increased in tumor cells. Thiamine uptake by the small intestines and by cells within various organs is mediated by a saturable, high affinity transport system. Alcohol affects thiamine uptake and other aspects of thiamine utilization, and these effects may contribute to the prevalence of thiamine deficiency in alcoholics. The major manifestations of thiamine deficiency in humans involve the cardiovascular (wet beriberi) and nervous (dry beriberi, or neuropathy and/or Wernicke-Korsakoff syndrome) systems. A number of inborn errors of metabolism have been described in which clinical improvements can be documented following administration of pharmacological doses of thiamine, such as thiamine-responsive megaloblastic anemia. Substantial efforts are being made to understand the genetic and biochemical determinants of inter-individual differences in susceptibility to development of thiamine deficiency-related disorders and of the differential vulnerabilities of tissues and cell types to thiamine deficiency.

Publication Types:
* Review
* Review, Tutorial

PMID: 11899071 [PubMed - indexed for MEDLINE]

4. Baker H, Hockstein S, DeAngelis B, Holland BK. Thiamin status of gravidas treated for gestational diabetes mellitus compared to their neonates at parturition. Int J Vitam Nutr Res. 2000 Dec;70(6):317-20.

Department of Preventive Medicine and Community Health, New Jersey Medical School, Newark, New Jersey, USA.

Since thiamin plays a role in glucose metabolism we wanted to know if blood thiamin influx from gravida to neonate was influenced by treatment of gravidas having gestational diabetes mellitus (GDM). In this study we found thiamin hypovitaminemia in 19% of the 77 pregnancies despite vitamin supplementation and treatment for GDM; neonates born to mothers with hypovitaminemia were also thiamin hypovitaminemic. All neonatal blood had significantly higher thiamin concentration than gravidas. Indeed, cord blood from neonates born to mothers treated with insulin for GDM had significantly higher thiamin concentration than other neonates in the study. A significant weight depression was noted in neonates born to treated GDM mothers. Healthy gravidas giving birth to macrosomia neonates, had significant thiamin hypovitaminosis, but only macrosomic neonates of treated diabetic mothers had significantly depressed blood thiamin concentrations.

We noted that subclinical thiamin hypovitaminemia is prominent during pregnancy despite vitamin supplementation. Perhaps increased thiamin supplementation during pregnancy seems warranted to avoid metabolic stress in mother and fetus due to thiamin hypovitaminemia.

PMID: 11214358 [PubMed - indexed for MEDLINE]

5. Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. Alcohol Clin Exp Res. 2001 Jan;25(1):112-6.

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BACKGROUND: Wernicke-Korsakoff syndrome (WKS) is most often seen in people who are alcohol dependent. Treatment with thiamin may rapidly resolve acute symptoms. However, much evidence suggests that identification of WKS on clinical examination is relatively insensitive when compared with diagnosis at postmortem. No study has investigated the therapeutic effect of thiamin in a sample of alcohol-dependent people without the clinical triad of acute WKS. METHODS: We conducted a randomized, double-blind, multidose study of thiamin treatment in 107 subjects who were detoxifying from alcohol. Five groups of subjects were assessed with the Mini-Mental State Examination and were examined for the presence of neurological signs. Subjects were given different doses of intramuscular thiamin for two consecutive days. The posttreatment performance of these groups then was examined on a test of working memory derived from comparative neuropsychology, namely, the delayed alternation task. This test has been established as sensitive to the neuropathology of WKS. RESULTS: Pretreatment measures of mental status and neurological signs were equivalent across groups. Groups were equated with respect to the background variables of age, education, typical daily alcohol consumption, and years of drinking. On the posttreatment measure, a superior performance was found in the group that received the highest dose of thiamin, compared with the other four treatment groups. CONCLUSIONS: A therapeutic relationship between dose and working memory performance was indicated. These results have important implications for the management and prevention of WKS, but further investigations are needed to substantiate the nature of the therapeutic relationship.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 11198705 [PubMed - indexed for MEDLINE]

VITAMIN B2 (RIBOFLAVIN)

Research has demonstrated a link between vitamin B2 deficiency or imbalance and the stress of exercise[1], brain and muscle function[2], treatment of Parkinson's disease[3], and also shows widespread deficiency in seniors[4].

The following description of Vitamin B2 is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

RIBOFLAVIN DEFICIENCY

Riboflavin (vitamin B2), as flavin mononucleotide or flavin adenine dinucleotide, acts as an essential coenzyme in many oxidation-reduction reactions involved with carbohydrate metabolism. Deficiency results in oral, ocular, cutaneous, and genital lesions.

Primary riboflavin deficiency is associated with inadequate consumption of milk and other animal products. Secondary deficiencies are most common in chronic diarrheas, liver disease, chronic alcoholism, and postoperative situations in which nutrient infusions lack supplementary vitamins.

Symptoms, Signs, and Laboratory Findings

The most common signs are pallor and maceration of the mucosa in the angles of the mouth (angular stomatitis) and vermilion surfaces of the lips (cheilosis), followed by superficial linear fissures that may leave scars when healed. When these lesions are infected by Candida albicans, grayish white exuberant lesions (perlèche) result. The tongue may appear magenta. Cutaneous lesions usually affect the nasolabial folds, alae nasi, ears, eyelids, scrotum, and labia majora. These areas become red, scaly, and greasy, and sebaceous material accumulates in hair follicles, producing dyssebacia or shark skin.

Rarely, neovascularization of the cornea and epithelial keratitis occur, resulting in lacrimation and photophobia. Nutritional amblyopia may respond to riboflavin.

Urinary excretion of < 30 μg riboflavin/g creatinine is associated with clinical signs of riboflavin deficiency. Increased activation of RBC glutathione reductase by riboflavin is an early sign of deficiency.

Diagnosis and Treatment

The lesions described do not occur solely in riboflavin deficiency. Cheilosis may result from vitamin B6 deficiency, edentulism, or ill-fitting dentures. Seborrheic dermatitis and ocular lesions may be produced by a number of conditions. Therefore, diagnosis of riboflavin deficiency cannot depend on the history and presence of suggestive lesions alone. Laboratory tests, elimination of other causes, and a therapeutic trial may be necessary.

Riboflavin 10 to 30 mg/day po in divided doses is given until a response is evident; then 2 to 4 mg/day is given until recovery. Riboflavin can be given in 5 to 20 mg/day in single or divided doses.

VITAMIN B2 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin B is "an essential coenzyme in many oxidation-reduction reactions involved with carbohydrate metabolism."

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B2 from lack of essential nutrients found in a whole foods diet, which leads to a host of health problems.

VITAMIN B2 REFERENCES

1. Manore MM. Effect of physical activity on thiamine, riboflavin, and vitamin B-6 requirements. Am J Clin Nutr. 2000 Aug;72(2 Suppl):598S-606S.

Food and Nutrition Laboratory, the Department of Family Resources and Human Development, Arizona State University, Tempe, AZ 85212, USA. melinda.manore@asu.edu

Because exercise stresses metabolic pathways that depend on thiamine, riboflavin, and vitamin B-6, the requirements for these vitamins may be increased in athletes and active individuals. Theoretically, exercise could increase the need for these micronutrients in several ways: through decreased absorption of the nutrients; by increased turnover, metabolism, or loss of the nutrients; through biochemical adaptation as a result of training that increases nutrient needs; by an increase in mitochondrial enzymes that require the nutrients; or through an increased need for the nutrients for tissue maintenance and repair. Biochemical evidence of deficiencies in some of these vitamins in active individuals has been reported, but studies examining these issues are limited and equivocal. On the basis of metabolic studies, the riboflavin status of young and older women who exercise moderately (2.5-5 h/wk) appears to be poorer in periods of exercise, dieting, and dieting plus exercise than during control periods. Exercise also increases the loss of vitamin B-6 as 4-pyridoxic acid. These losses are small and concomitant decreases in blood vitamin B-6 measures have not been documented. There are no metabolic studies that have compared thiamine status in active and sedentary persons. Exercise appears to decrease nutrient status even further in active individuals with preexisting marginal vitamin intakes or marginal body stores. Thus, active individuals who restrict their energy intake or make poor dietary choices are at greatest risk for poor thiamine, riboflavin, and vitamin B-6 status.

Publication Types:
* Review
* Review, Tutorial

PMID: 10919966 [PubMed - indexed for MEDLINE]

2. Baker SK, Tarnopolsky MA. Targeting cellular energy production in neurological disorders. Expert Opin Investig Drugs. 2003 Oct;12(10):1655-79.

Neurology and Rehabilitation, Room 4U4, Department of Medicine, McMaster University, Hamilton, Ontario, L8N 3Z5, Canada.

The concepts of energy dysregulation and oxidative stress and their complicated interdependence have rapidly evolved to assume primary importance in understanding the pathophysiology of numerous neurological disorders. Therefore,

neuroprotective strategies addressing specific bioenergetic defects hold particular promise in the treatment of these conditions (i.e., amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Friedreich's ataxia, mitochondrial cytopathies and other neuromuscular diseases), all of which, to some extent, share 'the final common pathway' leading to cell death through either necrosis or apoptosis. Compounds such as creatine monohydrate and coenzyme Q(10) offer substantial neuroprotection against ischaemia, trauma, oxidative damage and neurotoxins. Miscellaneous agents, including alpha-lipoic acid, beta-OH-beta-methylbutyrate, riboflavin and nicotinamide, have also been shown to improve various metabolic parameters in brain and/or muscle. This review will highlight the biological function of each of the above mentioned compounds followed by a discussion of their utility in animal models and human neurological disease. The balance of this work will be comprised of discussions on the therapeutic applications of creatine and coenzyme Q(10).

Publication Types:
* Review
* Review, Tutorial

PMID: 14519086 [PubMed - indexed for MEDLINE]

3. Coimbra CG, Junqueira VB. High doses of riboflavin and the elimination of dietary red meat promote the recovery of some motor functions in Parkinson's disease patients. Braz J Med Biol Res. 2003 Oct;36(10):1409-17. Epub 2003 Sep 16.

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Abnormal riboflavin status in the absence of a dietary deficiency was detected in 31 consecutive outpatients with Parkinson's disease (PD), while the classical determinants of homocysteine levels (B6, folic acid, and B12) were usually within normal limits. In contrast, only 3 of 10 consecutive outpatients with dementia without previous stroke had abnormal riboflavin status. The data for 12 patients who did not complete 6 months of therapy or did not comply with the proposed treatment paradigm were excluded from analysis. Nineteen PD patients (8 males and 11 females, mean age +/- SD = 66.2+/-8.6 years; 3, 3, 2, 5, and 6 patients in Hoehn and Yahr stages I to V) received riboflavin orally (30 mg every 8 h) plus their usual symptomatic medications and all red meat was eliminated from their diet. After 1 month the riboflavin status of the patients was normalized from 106.4+/-34.9 to 179.2+/-23 ng/ml (N = 9). Motor capacity was measured by a modification of the scoring system of Hoehn and Yahr, which reports motor capacity as percent. All 19 patients who completed 6 months of treatment showed improved motor capacity during the first three months and most reached a plateau while 5/19 continued to improve in the 3- to 6-month interval. Their average motor capacity increased from 44 to 71% after 6 months, increasing significantly every month compared with their own pretreatment status ($P < 0.001$, Wilcoxon signed rank test). Discontinuation of riboflavin for several days did not impair motor capacity and yellowish urine was the only side effect observed. The data show that the proposed treatment improves the clinical condition of PD patients. Riboflavin-sensitive mechanisms involved in PD may include glutathione depletion, cumulative mitochondrial DNA mutations, disturbed mitochondrial protein complexes, and abnormal iron metabolism. More studies are required to identify the mechanisms involved.

PMID: 14502375 [PubMed - indexed for MEDLINE]

4. Wolters M, Hermann S, Hahn A. B vitamin status and concentrations of homocysteine and methylmalonic acid in elderly German women. Am J Clin Nutr. 2003 Oct;78(4):765-72.

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BACKGROUND: Prior investigations found that elderly persons are at higher risk than are younger persons for B vitamin deficiency, which leads to elevated plasma total homocysteine (tHcy) concentrations that are associated with an increased risk for certain diseases such as coronary artery disease. To date, published data have shown decreased vitamin status and elevated tHcy among the elderly. OBJECTIVE: We evaluated the dietary intake and the blood status of various B vitamins and tHcy and methylmalonic acid (MMA) concentrations in 178 younger (60-70-y-old) female seniors. DESIGN: Dietary intake was assessed with a 3-d diet record. Thiamine, riboflavin, and vitamin B-6 activity coefficients of erythrocyte transketolase (EC 2.2.1.1), erythrocyte glutathione reductase (EC 1.6.4.2), and erythrocyte alpha-aspartic aminotransferase (EC 2.6.1.1) were used as functional indexes for the status of the 3 vitamins, respectively. Concentrations of serum and red blood cell folate, serum cobalamin and MMA, and plasma tHcy were measured. RESULTS: Indexes of thiamine, pyridoxine, and cobalamin indicated insufficient status in one-third of the women, whereas tHcy and MMA concentrations were elevated in 17.4% and 9.6% of the women, respectively. An association between vitamin intake and vitamin concentration in the blood was found only for folate. The mean tHcy concentration in subjects in the lowest quartile of serum folate concentration was 23% higher than that in subjects in the highest quartile. There was no association between riboflavin and tHcy concentrations. MMA was positively correlated with age and inversely correlated with serum cobalamin concentration. CONCLUSIONS: Even in younger, well-educated, female seniors, the prevalence of low B vitamin status and elevated plasma tHcy concentration is high. Thiamine, pyridoxine, folate, and cobalamin supplementation should be considered.

PMID: 14522735 [PubMed - indexed for MEDLINE]

VITAMIN B3 (NIACINAMIDE)

Research has demonstrated a link between vitamin B3 deficiency or imbalance and schizophrenia[1], nerve cell survival[2], stress[3], neuroprotection[4,5], brain ischemia[6], protection after spinal cord injury[7].

The following description of Vitamin B3 is taken from The Merck Manual of Diagnosis and Therapy (Seventeenth Edition).

NIACIN DEFICIENCY

Niacin (nicotinic acid) derivatives include nicotinamide adenine dinucleotide (NAD, coenzyme I) and nicotinamide adenine dinucleotide phosphate (NADP, coenzyme II), which are coenzymes in oxidation-reduction reactions. They are vital in cell metabolism.

ETIOLOGY

Severe deficiencies of niacin and tryptophan, a precursor from which the body can synthesize niacin, are the principal causes of **pellagra**. **Primary deficiency** usually occurs in areas where maize (Indian corn) forms a major part of the diet. Bound niacin, found in maize, is not assimilated in the intestinal tract unless it has been previously treated with alkalis, as in the preparation of tortillas. Corn protein is also deficient in tryptophan. Amino acid imbalance may also contribute to deficiency, since pellagra is common in India among persons who eat a millet with a high leucine content.

Secondary deficiency occurs in diarrheas, cirrhosis, and alcoholism as well as after extensive postoperative use of nutrient infusions lacking vitamins. Pellagra may occur during prolonged isoniazid therapy (the drug replaces niacinamide in NAD), in malignant carcinoid tumor (tryptophan is diverted to form 5-hydroxytryptamine), and in Hartnup disease (see Anomalies in Kidney Transport in Ch. 261).

Symptoms and Signs

Pellagra is characterized by cutaneous, mucous membrane, CNS, and GI symptoms. The complete syndrome of advanced deficiency includes symmetric photosensitive rash, scarlet stomatitis, glossitis, diarrhea, and mental aberrations. Symptoms may appear alone or in combination.

Four types of **cutaneous lesions**, usually bilaterally symmetric, are recognized:

1. Acute lesions consisting of erythema followed by vesiculation, bullae, crusting, and desquamation; secondary infection is common, notably after exposure to sunlight (actinic trauma)

2. Intertrigo, also acute, characterized by redness, maceration, abrasion, and secondary infection in the intertriginous areas

3. Chronic hypertrophy, in which the skin is thickened, inelastic, fissured, and deeply pigmented over pressure points; secondary infection often develops, and the lesion has a sharply defined pearly border of regenerating epithelium when healing begins

4. Chronic atrophic lesions, with dry, scaly, inelastic skin too large for the part it covers (seen in older pellagrins).

The distribution of lesions--at trauma points--is more characteristic than their form. Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

Mucous membrane symptoms primarily affect the mouth but may also affect the vagina and urethra. Scarlet glossitis and stomatitis are characteristic of acute deficiency. The tip and margins of the tongue and the mucosa around Stensen's duct are affected first. As the lesion progresses, the entire tongue and oral mucous membranes become bright scarlet, followed by a sore mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth. They are often covered by a grayish slough containing Vincent's organisms.

GI symptoms, which are indeterminate in early cases, include burning of the mouth, pharynx, and esophagus and abdominal discomfort and distention. Later, nausea, vomiting, and diarrhea may occur. Diarrhea, often bloody because of GI hyperemia and ulceration, is serious.

CNS symptoms include (1) organic psychosis, characterized by memory impairment, disorientation, confusion, and confabulation (excitement, depression, mania, and delirium predominate in some patients; in others, the reaction is paranoid); and (2) encephalopathic syndrome, characterized by clouding of consciousness, cogwheel rigidity of the extremities, and uncontrollable sucking and grasping reflexes. Differentiating these CNS changes from those in thiamine deficiency is difficult.

Diagnosis and Treatment

Niacin deficiency must be distinguished from other causes of stomatitis, glossitis, diarrhea, and dementia. Diagnosis is easy when the clinical findings include skin and mouth lesions, diarrhea, delirium, and dementia. More often, the condition is less fully developed, and a history of a diet lacking niacin and tryptophan is significant. Urinary excretion of N′-methylnicotinamide (NMN) and its pyridone is decreased. NMN excretion of < 0.8 mg/day suggests a niacin deficiency.

Multiple deficiencies of B vitamins and protein often occur together; therefore, a balanced diet is needed. Supplemental niacinamide 300 to 1000 mg/day should be given orally in divided doses. In most cases, 300 to 500 mg is sufficient. Niacinamide is generally used to treat deficiency states, because niacin can cause flushing, itching, burning, or tingling sensations, whereas niacinamide does not; however, niacinamide does not possess hypolipidemic or vasodilating properties as does niacin. When oral therapy is precluded because of diarrhea or lack of patient cooperation, 100 to 250 mg should be injected sc bid to tid. In encephalopathic states, 1000 mg po plus 100 to 250 mg IM is recommended. Other B-complex vitamins should also be given in therapeutic dosages.

VITAMIN B3 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin B3 acts in various coenzymes responsible for oxidation-reduction reactions and are vital in cell metabolism. The Merck Manual goes on to define severe vitamin B3 deficiency as a condition called pellagra. It fails to define mild deficiency or to suggest that the best form of

differentiating the lesions of pellagra from other diseases would be to offer a trial of vitamin B3 therapy.

The central nervous system symptoms are especially notable including "memory impairment, disorientation, confusion" which are common in the elderly. The question is not asked or answered as to whether the increased symptoms of mild dementia in our aging population might be due to vitamin B3 (and other nutrient) deficiency.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B3 from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

VITAMIN B3 REFERENCES

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PMID: 7040274

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Division of Cellular and Molecular Cerebral Ischemia, Center for Molecular Medicine and Genetics, Institute of Environmental Health Sciences, Wayne State University School of Medicine, Detroit, Michigan 48201, USA.

Nicotinamide, a beta-nicotinamide adenine dinucleotide (NAD) precursor and an essential nutrient for cell growth and function, may offer critical insights into the specific cellular mechanisms that determine neuronal survival, since this agent significantly impacts upon both neuronal and vascular integrity in the central nervous system. The authors show that nicotinamide provides broad, but concentration-specific, protection against apoptotic genomic DNA fragmentation and membrane phosphatidylserine exposure during oxidative stress to secure cellular integrity and prevent phagocytic cellular demise. Activation of the protein kinase B (Akt1) pathway is a necessary requirement for nicotinamide protection, because transfection of primary hippocampal neurons with a plasmid encoding a kinase-deficient dominant-negative Akt1 as well as pharmacologic inhibition of phosphatidylinositol-3-kinase phosphorylation of Akt1 eliminates cytoprotection by nicotinamide. Nicotinamide fosters neuronal survival through a series of intimately associated pathways. At one level, nicotinamide directly modulates mitochondrial membrane potential and pore formation to prevent cytochrome c release and caspase-3-and 9-like activities through mechanisms that are independent of the apoptotic protease activating factor-1. At a second level, nicotinamide maintains an inhibitory phosphorylation of the forkhead transcription factor FOXO3a at the regulatory sites of Thr and Ser and governs a unique regulatory loop that prevents the degradation of phosphorylated FOXO3a by caspase-3. Their work elucidates

some of the unique neuro-protective pathways used by the essential cellular nutrient nicotinamide that may direct future therapeutic approaches for neurodegenerative disorders.

PMID: 15241181 [PubMed - indexed for MEDLINE]

3. Okamoto H, Ishikawa A, Yoshitake Y, Kodama N, Nishimuta M, Fukuwatari T, Shibata K. Diurnal variations in human urinary excretion of nicotinamide catabolites: effects of stress on the metabolism of nicotinamide. J Clin Nutr. 2003 Feb;77(2):406-10.

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BACKGROUND: More than 500 enzymes need niacin coenzymes. Therefore, elucidation of the control mechanisms of coenzyme metabolism is fundamentally important. OBJECTIVE: NAD(+) is involved in ATP production. Because energy expenditure is generally higher during the day than at night, we investigated whether the metabolism of nicotinamide changes at various times of day and whether stress affects nicotinamide metabolism. DESIGN: Twelve women were housed in the same facility and followed the same schedule for activities of daily living for 12 d. Urinary outputs were collected during 5 specific periods to investigate diurnal variations in nicotinamide metabolism. The effects of cold exposure (physical stress), having to perform arithmetic calculations (mental stress), and dark exposure (emotional stress) on nicotinamide metabolism were investigated. RESULTS: A diurnal variation in the nicotinamide metabolites N(1)-methylnicotinamide, N(1)-methyl-2-pyridone-5-carboxamide, and N(1)-methyl-4-pyridone-3-carboxamide was observed. Of the stresses studied, cold exposure significantly increased the urinary excretory outputs of the nicotinamide metabolites. CONCLUSIONS: Diurnal variations in nicotinamide metabolism were found in these women. The biosynthesis of nicotinamide from tryptophan seemed to be increased by cold exposure.

Publication Types:
* Clinical Trial
* Controlled Clinical Trial

PMID: 12540401 [PubMed - indexed for MEDLINE]

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Department of Molecular Pharmacology and Toxicology, University of Southern California, School of Pharmacy, 1985 Zonal Avenue, PSC 508, Los Angeles, CA 90089-9121, USA.

Pyridine nucleotides are critical during oxidative stress due to their roles in reductive reactions and energetics. The aim of the present study was to examine pyridine nucleotide changes in six brain regions of mice after an intracerebroventricular injection of the oxidative stress inducing agent, t-butyl hydroperoxide (t-BuOOH). A secondary aim was to investigate the correlation between NAD+ levels and DNA fragmentation. Here, we demonstrate that t-

BuOOH induced a rapid oxidation of NADPH and a slow depletion of NAD+ in most brain regions. A slight increase in NADH also occurred in five brain regions. NAD+ depletion was associated with increased DNA fragmentation. This suggests the initiation of a death cascade involving poly(ADP-ribose) polymerase (PARP), NAD+, ATP depletion and consequent cell death in brain tissue. PARP activity was accelerated in some brain regions after 20 min of oxidative stress. To counteract oxidative stress induced toxicity, NAD+ levels were increased in the brain using an intraperitoneal injection of nicotinamide. A surplus of brain NAD+ prevented DNA fragmentation in some brain regions. Nicotinamide administration also resulted in higher brain NADH, NADP+ and NADPH levels in some regions. Their synthesis was further upregulated during oxidative stress. Nicotinamide as a precursor for NAD+ may provide a useful therapeutic strategy in the treatment of neurodegeneration.

PMID: 11342263 [PubMed - indexed for MEDLINE]

5. Gupta S, Kaul CL, Sharma SS. Neuroprotective effect of combination of poly (ADP-ribose) polymerase inhibitor and antioxidant in middle cerebral artery occlusion induced focal ischemia in rats. Neurol Res. 2004 Jan;26(1):103-7.

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar (Mohali) 160 062, Punjab, India.

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Punjab, India We have investigated the neuroprotective potential of combination of poly (ADP-ribose) polymerase inhibitor (nicotinamide or 3-aminobenzamide) and antioxidant (melatonin) in middle cerebral artery occlusion (MCAo) induced focal ischemia in rats. MCAo of 2 h followed by 22 h reperfusion produced large volume of cerebral infarction (mean +/- SEM 211.38 +/- 8.35 mm3), volume of edema (60 +/- 2 mm3) and neurological deficits (4.45 +/- 0.25). Combination of nicotinamide (500 mg kg(-1), i.p.) and melatonin (10 mg kg(-1), i.p.) significantly decreased infarct volume to 48 +/- 2.58 mm3 as compared to their individual drug (nicotinamide 76 +/- 12.49mm3, melatonin 76.17 +/- 1.24 mm3). A significant improvement was observed in edema volume and neurological deficits with this combination. Combination of 3-aminobenzamide (20 mg kg(-1), i.p.) and melatonin (10 mg kg(-1), i.p.) also produced similar reduction in infarction, edema and neurological score. These results indicate that the combination of poly (ADP-ribose) polymerase inhibitor and antioxidant produce enhanced neuroprotection. Clinical availability and wide therapeutic margin of nicotinamide and melatonin make them a promising drug combination for clinical evaluation in stroke patients.

PMID: 14977067 [PubMed - indexed for MEDLINE]

6. Sadanaga-Akiyoshi F, Yao H, Tanuma S, Nakahara T, Hong JS, Ibayashi S, Uchimura H, Fujishima M. Nicotinamide attenuates focal ischemic brain injury in rats: with special reference to changes in nicotinamide and NAD+ levels in ischemic core and penumbra. Neurochem Res. 2003 Aug;28(8):1227-34.

Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. kamefu@rb-3.so-net.ne.jp

We investigated the neuroprotective action of nicotinamide in focal ischemia. Male spontaneously hypertensive rats (5-7 months old) were subjected to photothrombotic occlusion of the right distal middle cerebral artery (MCA). Either nicotinamide (125 or 250 mg/kg) or vehicle was injected i.v. before MCA occlusion. Changes in the cerebral blood flow (CBF) were monitored using laser-Doppler flowmetry, and infarct volumes were determined with TTC staining 3 days after MCA occlusion. In another set of experiments, the brain nicotinamide and nicotinamide adenine dinucleotide (NAD+) levels were analyzed by HPLC using the frozen samples dissected from the regions corresponding to the ischemic core and penumbra. In the 250-mg/kg nicotinamide group, the ischemic CBF was significantly increased compared to that the untreated group, and the infarct volumes were substantially attenuated (-36%). On the other hand, the ischemic CBF in the 125 mg/kg nicotinamide group was not significantly different from the untreated CBF, however, the infarct volumes were substantially attenuated (-38%). Cerebral ischemia per se did not affect the concentrations of nicotinamide and NAD+ both in the penumbra and ischemic core. In the nicotinamide groups, the brain nicotinamide levels increased significantly in all areas examined, and brain NAD+ levels increased in the penumbra but not in the ischemic core. Increased brain levels of nicotinamide are considered to be primarily important for neuroprotection against ischemia, and the protective action may be partly mediated through the increased NAD+ in the penumbra.

PMID: 12834263 [PubMed - indexed for MEDLINE]

7. Brewer KL, Hardin JS. Neuroprotective effects of nicotinamide after experimental spinal cord injury. Acad Emerg Med. 2004 Feb;11(2):125-30.

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OBJECTIVE: To investigate the ability of nicotinamide to protect against secondary damage in spinal cord tissue after an experimental injury. Trauma to the spinal cord induces a cascade of cellular events that lead to progressive tissue injury over time. Nicotinamide has been shown to affect many elements of this cascade, including excitatory amino acid release, inflammation, apoptosis, and cellular energy balance. METHODS: Male Long-Evans (n = 12) rats received an excitotoxic spinal cord injury by intraspinal injection of quisqualic acid (QUIS), a glutamate receptor agonist. A second set of rats (n = 4) received intraspinal saline as a sham injury. Thirty minutes after injury, animals that had QUIS injections received an intraperitoneal injection of either saline (control, n = 4) or nicotinamide (500 mg/kg, n = 8). Seven days postinjury, the spinal cords were removed, and serial sections were cut, mounted on slides, and stained. By using light microscopy, the extent of tissue damage was assessed at the epicenter of injury as well as sections up to 450- microm rostral and 450- microm caudal to the epicenter. RESULTS: Only those animals receiving QUIS injections showed damaged tissue. There was no significant difference in the amount of damage at the epicenter of injury between the saline- and nicotinamide-treated animals. However, when comparing the total amounts of damage over the 975- microm length of cord examined, the rostro-caudal extent of injury was significantly reduced in the nicotinamide-treated animals compared with the saline-treated animals.

CONCLUSIONS: Systemic nicotinamide serves to limit the rostro-caudal extent of cell death after experimental spinal cord injury.

PMID: 14759952 [PubMed - indexed for MEDLINE]

VITAMIN B5 (D-CALCIUM PANTOTHENATE)

Research has demonstrated a link between vitamin B5 deficiency or imbalance and generalized malaise[1], aging[2], and glutathione levels[3].

The following description of Vitamin B5 is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

PANTOTHENIC ACID DEFICIENCY

Pantothenic acid is a vitamin widely distributed in foodstuffs and is an essential component of coenzyme A, which functions as an acyltransfer cofactor for many enzymatic reactions. Adults probably require about 4 to 7 mg/day, corresponding to a whole blood level of 100 to 180 μg/dL (4.56 to 8.21 μmol/L), but no RDA has been set. Pantothenic acid deficiency is rarely observed in humans.

Adult volunteers on a deficient diet experienced malaise, abdominal discomfort, and burning feet associated with paresthesias, which responded to pantothenic acid. In clinical practice, however, these nonspecific symptoms rarely respond to the vitamin.

VITAMIN B5 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation vitamin B5 "is an essential component of coenzyme A, which functions as an acyltransfer cofactor for many enzymatic reactions". This brief entry minimizes the very important nature of this vitamin.

According to basic science texts, coenzyme A (CoA) is adapted from pantothenic acid and adenosine triphosphate and used in metabolism in areas such as fatty acid oxidation and the citric acid cycle. Its main function is to carry acyl groups such as acetyl as thioesters. A molecule of coenzyme A carrying an acetyl group is also referred to as acetyl-CoA. The importance of vitamin B5 is then transmitted to acetyl-CoA as a precursor to HMG CoA, which is a vital component in cholesterol and ketone synthesis. It also contributes the *acetyl* group to the extremely important acetylcholine. Acetylcholine is the neurotransmitter responsible for all muscle activity.

According to Italian vitamin researcher, Dr. Alberto Fidanza, vitamin B5 is "important for adrenal activity, stimulates tissue regeneration, anti inflammatory action". It also, "Normalises motility of intestine and has a protective function against atherosclerosis". (Fidenza A. The Protective Actions of Vitamins from "Le Vitamine" Third Edition. 1997). Professor Fidanza published dozens of papers on vitamins with a special focus on pantothenic acid. His work was mostly confined to the 1970s and 1980s. There is a dearth of scientific studies on pantothenic acid in humans in the past two decades.

The Merck Manual is quick to suggest that vitamin B5 deficiency is rare in humans. Yet they do say that "Adult volunteers on a deficient diet experienced malaise, abdominal discomfort, and burning feet associated with paresthesias, which responded to pantothenic acid."

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding

generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B5 from lack of essential nutrients found in a whole foods diet, which leads to a host of health problems.

VITAMIN B5 REFERENCES

1. Tahiliani AG, Beinlich CJ. Pantothenic acid in health and disease. Vitam Horm. 1991;46:165-228.

Geisinger Clinic, Weis Center for Research, Danville, Pennsylvania 17822.

In summary, the vitamin pantothenic acid is an integral part of the acylation carriers, CoA and acyl carrier protein (ACP). The vitamin is readily available from diverse dietary sources, a fact which is underscored by the difficulty encountered in attempting to induce pantothenate deficiency. Although pantothenic acid deficiency has not been linked with any particular disease, deficiency of the vitamin results in generalized malaise clinically. In view of the fact that pantothenate is required for the synthesis of CoA, it is surprising that tissue CoA levels are not altered in pantothenate deficiency. This suggests that the cell is equipped to conserve its pantothenate content, possibly by a recycling mechanism for utilizing pantothenate obtained from degradation of pantothenate-containing molecules. Although the steps involved in the conversion of pantothenate to CoA have been characterized, much remains to be done to understand the regulation of CoA synthesis. In particular, in view of what is known about the in vitro regulation of pantothenate kinase, it is surprising that the enzyme is active in vivo, since factors that are known to inhibit the enzyme are present in excess of the concentrations known to inhibit the enzyme. Thus, other physiological regulatory factors (which are largely unknown) must counteract the effects of these inhibitors, since the pantothenate-to-CoA conversion is operative in vivo. Another step in the biosynthetic pathway that may be rate limiting is the conversion of 4'-phosphopantetheine (4'-PP) to dephospho-CoA, a step catalyzed by 4'-phosphopantetheine adenylyl-transferase. In mammalian systems, this step may occur in the mitochondria or in the cytosol. The teleological significance of these two pathways remains to be established, particularly since mitochondria are capable of transporting CoA from the cytosol. Altered homeostasis of CoA has been observed in diverse disease states including starvation, diabetes, alcoholism, Reye syndrome (RS), medium-chain acyl CoA dehydrogenase deficiency, vitamin B12 deficiency, and certain tumors. Hormones, such as glucocorticoids, insulin, and glucagon, as well as drugs, such as clofibrate, also affect tissue CoA levels. It is not known whether the abnormal metabolism observed in these conditions is the result of altered CoA metabolism or whether CoA levels change in response to hormonal or nonhormonal perturbations brought about in these conditions. In other words, a cause-effect relation remains to be elucidated. It is also not known whether the altered CoA metabolism (be it cause or result of abnormal metabolism) can be implicated in the manifestations of a disease. Besides CoA, pantothenic acid is also an integral part of the ACP molecule. (ABSTRACT TRUNCATED AT 400 WORDS)

Publication Types:
* Review
* Review, Academic

PMID: 1746161 [PubMed - indexed for MEDLINE]

2. Ames BN. Delaying the mitochondrial decay of aging. Ann N Y Acad Sci. 2004 Jun;1019:406-11.

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Mitochondrial dysfunction may be a principal underlying event in aging, including the degenerative diseases of aging such as brain degeneration. Mitochondria provide energy for basic metabolic processes, and their decay with age impairs cellular metabolism and leads to cellular decline. Progress over the last decade in delaying the mitochondrial decay of aging is reviewed.

Publication Types:
* Review
* Review, Tutorial

PMID: 15247055 [PubMed - indexed for MEDLINE]

3. Slyshenkov VS, Dymkowska D, Wojtczak L. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. EBS Lett. 2004 Jul 2;569(1-3):169-72.

Nencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland.

We have previously observed (summarized in BioFactors 17 (2003) 61) that pantothenic acid, pantothenol and other derivatives that are precursors of CoA protect cells and whole organs against peroxidative damage by increasing the content of cell glutathione. The present investigation was aimed to elucidate the mechanism of this increase in human lymphoblastoic (Jurkat) cells. It showed that incubation of the cells with pantothenic acid or pantothenol increased mainly the content of free glutathione, with little effect on protein-bound glutathione. Buthionine sulfoximine, an inhibitor of glutathione synthesis, prevented this increase. Increase of the content of free glutathione, as produced by pantothenic acid or pantothenol, was largely prevented by respiratory chain inhibitor rotenone, inhibitor of mitochondrial ATP synthesis oligomycin and uncoupler of oxidative phosphorylation of carbonyl cyanide 3-chlorophenylhydrazone. These treatments also decreased the cellular content of ATP. Preincubation with pantothenic acid or pantothenol also increased cell respiration with pyruvate as the exogenous substrate. Although no significant increase of total cell CoA content could be found, it is concluded that the increase of the glutathione level was due to increased production of ATP that was, in turn, a result of the increased content of mitochondrial CoA.

PMID: 15225628 [PubMed - indexed for MEDLINE]

VITAMIN B6 (PYRIDOXINE HYDROCHLORIDE)

Studies have shown an association between a lack of Vitamin B6 or imbalance and schizophrenia[1], aging[2], and homocysteinuria[3].

The following description of Vitamin B6 is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

VITAMIN B6 DEFICIENCY AND DEPENDENCY

Vitamin B6 comprises a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine. They are metabolized and phosphorylated in the body to pyridoxal phosphate, which functions as a coenzyme in many reactions, including decarboxylation and transamination of amino acids, deamination of hydroxyamino acids and cysteine, conversion of tryptophan to niacin, and metabolism of fatty acids. Consequently, the vitamin B6 group is important in blood, CNS, and skin metabolism. Vitamin B6 is important in erythropoiesis because pyridoxal phosphate is needed in the formation of -aminolevulinic acid, the rate-limiting step in heme biosynthesis.

Primary deficiency is rare, because most foods contain vitamin B6. Nonetheless, an outbreak of convulsions in infants did follow the inadvertent destruction of vitamin B6 in infant formulas. **Secondary deficiency** may result from malabsorption, alcoholism, oral contraceptive use, chemical inactivation by drugs (eg, isonicotinic acid hydrazide, cycloserine, hydralazine, penicillamine), excessive loss, and increased metabolic activity.

Symptoms and Signs

Deficiency: The vitamin B6 antagonist deoxypyridoxine produces seborrheic dermatosis, glossitis, cheilosis, peripheral neuropathy, and lymphopenia. Vitamin B6 deficiency can cause convulsions in infants and anemia in adults (usually normocytic but occasionally microcytic).

Laboratory Findings and Diagnosis

At present, there is no generally accepted test of vitamin B6 status. The whole blood level of pyridoxal phosphate is a better indicator than the plasma level. Erythrocyte glutamic pyruvate and oxaloacetic transaminase activities are decreased in vitamin B6 deficiency, but these changes are not diagnostic because of the wide range of values in healthy persons.

Treatment

Underlying causes such as use of pyridoxine-inactivating drugs (anticonvulsants, corticosteroids, estrogens, isoniazid, penicillamine, and hydralazine) or malabsorption should be corrected. For **dependency in infants**, the daily requirement (normally 0.4 mg) is increased many times (up to 10 mg). For pyridoxine-dependent seizures, the initial dose is 50 to 100 mg IM or IV daily for 1 wk followed by oral doses tapered over 1 wk to 25 mg. **Deficiency in adults** usually responds to pyridoxine 50 to 100 mg/day po. Conditions that increase metabolic demand, such as hyperthyroidism and diabetes, require amounts in excess of the recommended allowance. For pyridoxine deficiency associated with drugs such as isoniazid, 100 mg/day may be required. For **dependency in adults**, as much as 200 to 600 mg daily of pyridoxine may be needed.

VITAMIN B6 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin B6 is responsible for a remarkable number of functions in the body. The authors insist, however, that vitamin B6 deficient is rare because it is found in many foods.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B6 from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

The Merck Manual also states that deficiency states can occur in people who suffer from "malabsorption, alcoholism, oral contraceptive use, chemical inactivation by drugs…, and increased metabolic activity", which we find are very common conditions in the general population. We also note the vast amount of research that has identified vitamins B6, B9 (folic acid), and B12 as the essential nutrients necessary to decrease the levels of homocysteine in the blood. Homocysteinuria is now regarded as a more important risk factor for heart disease than cholesterol. It seems that everyone in the population could benefit from taking adequate amounts of the B vitamin complex.

VITAMIN B6 TOXICITY

The ingestion of megadoses (2 to 6 g/day for 2 to 40 mo) of pyridoxine, mistakenly taken for premenstrual tension, may cause progressive sensory ataxia and profound lower limb impairment of position and vibration sense. Senses of touch, temperature, and pain are less affected. The motor and central nervous systems are unimpaired. Recovery is slow and, in some patients, is only partial after pyridoxine ingestion is stopped.

VITAMIN B6 REFERENCES

1. Petrie WM, Ban TA, Ananth JV. The use of nicotinic acid and pyridoxine in the treatment of schizophrenia. Int Pharmacopsychiatry; 16(4):245-50. 1981

PMID: 7040274

2. Stern F, Berner YN, Polyak Z, Bernadiner S, Komarnitsky M, Sela BA, Doolman R, Dror Y.

Nutritional status and vitamin B6 supplementation in the institutionalized elderly. Harefuah. 2000 Aug;139(3-4):97-102, 167, 166.

Institute of Biochemistry, Food Science, and Nutrition, Hebrew University of Jerusalem.

Nutritional status and vitamin B6 status were assessed in 18 men and 32 women, average age 84, living in a home for the aged. Average proportion of energy derived from protein was higher than the recommended; fiber intake was very low. Also low were intakes of calcium, magnesium, zinc, copper, vitamins D and E, thiamin, folic acid and vitamin B6. Supplementation with vitamin B6 (10 mg/d) for 28 days

in those with the lowest B6 status assessed by B6 intake, activation coefficient of aspartate transaminase and plasma pyridoxamine concentrations led to improved B6 status (marked decrease in activation coefficient) and increased synthesis and decreased degradation of many short-lived neutrophil proteins. Though our elderly enjoy a variety of foods, some have marginal deficiencies that can be improved. Therefore, in the institutionalized elderly, micronutrient supplementation should be administered at a level low enough to be safe (below recommended upper level of intake) but high enough to be effective.

PMID: 10979465 [PubMed - indexed for MEDLINE]

3. Wolters M, Hermann S, Hahn A. Effect of multivitamin supplementation on the homocysteine and methylmalonic acid blood concentrations in women over the age of 60 years. Eur J Nutr. 2004 May 19;:1-10.

Nutrition Physiology & Human Nutrition Unit, Institute of Food Science Centre of Applied Chemistry University of Hanover, Wunstorfer Str. 14, 30453, Hannover, Germany.

BACKGROUND. Deficiency of folic acid, vitamin B(6) and/or vitamin B(12) can result in elevated total plasma homocysteine concentrations (tHcy), which are considered to be a risk factor for vascular disease. Studies have shown that supplementation of the three vitamins can lower tHcy even in subjects with tHcy in the normal range. AIM OF THE STUDY. The aim of this study was to evaluate the effect of a 6 month supplementation with vitamin B(6), B(12) and folate on the concentrations of total plasma homocysteine and serum methylmalonic acid (MMA) of elderly women. METHODS. The study was designed as a randomized placebo controlled doubleblind trial, and 220 healthy women (aged 60-91 years) were involved. The vitamin and mineral capsule contained pyridoxine (3.4 mg), folic acid (400 micro g) and cobalamin (9 micro g) in addition to other micronutrients. Blood concentrations of folate, cobalamin, tHcy, MMA and the activity coefficient of erythrocyte alpha-aspartic aminotransferase (alpha-EAST) were measured at baseline and after 6 months of supplementation. Dietary intake was evaluated at the beginning and the end of the intervention by two 3-day diet records. RESULTS. Median concentrations of serum cobalamin, serum folate and erythrocyte folate increased significantly and tHcy and alpha-EAST activity (indicative of improved status of vitamin B(6)) coefficient decreased significantly in the supplemented group. Median MMA concentration of the supplemented group was significantly lower than that of the placebo group after the intervention. The vitamin supplementation had a greater decreasing effect on the tHcy concentration of volunteers with lower vitamin and higher tHcy initial concentrations. In a linear regression model, baseline tHcy, serum folate, age and alpha-EAST activity coefficient were significantly correlated with the change in tHcy. The change in MMA in the supplement group was significantly associated to the baseline MMA values. CONCLUSIONS. Our results show that a 6 month supplementation including physiological dosages of B vitamins improves the status of these nutrients and reduces tHcy in presumed healthy elderly women.

PMID: 15309436 [PubMed - as supplied by publisher]

VITAMIN B9 (FOLIC ACID)

Research has demonstrated a link between vitamin B9 deficiency or imbalance and dementia[1], cognitive function[2], and depression[3,4,5].

The following description of Vitamin B9 is taken from *The Merck Manual Second Home Edition.*

Folic acid (folate), with vitamin B12, is necessary for the formation of normal red blood cells and the synthesis of DNA, the genetic material of cells.

FOLIC ACID DEFICIENCY

Because the body stores only a small amount of folic acid (folate), a diet lacking in folic acid leads to a deficiency within a few months. Folic acid deficiency is common because many people do not eat enough raw leafy vegetables or citrus fruits. Undernutrition associated with alcoholism is a common cause. Also, alcohol consumed in large amounts interferes with the absorption and processing (metabolism) of folic acid. Certain anticonvulsants (such as phenytoin and phenobarbital) and drugs used to treat ulcerative colitis (such as sulfasalazine) decrease the absorption of this vitamin. Methotrexate (used to treat cancer and rheumatoid arthritis) and trimethoprim-sulfamethoxazole (an antibiotic) interfere with the metabolism of folic acid.

Women who are pregnant or breastfeeding and people undergoing dialysis may develop this deficiency, because their need for folic acid is increased.

Symptoms, Diagnosis, and Treatment

People who have folic acid deficiency develop anemia similar to that due to vitamin B12 deficiency.

Fatigue may be the first symptom. In addition to the general symptoms of anemia (such as paleness, irritability, shortness of breath, and dizziness), folic acid deficiency may cause a red and sore tongue, a reduced sense of taste, weight loss, and diarrhea. If a pregnant woman has folic acid deficiency, the baby may have a birth defect of the spinal cord (neural tube defect).

If a blood test detects large red blood cells in a person who has anemia or who is undernourished, doctors measure the folic acid level in a blood sample. A low level indicates this deficiency.

Treatment consists of taking daily doses of a folic acid supplement. People who are taking drugs that interfere with the absorption or metabolism of folic acid should take a folic acid supplement as a preventive measure. Women who are pregnant or who are planning to become pregnant should take higher doses to reduce the risk of having a baby with a birth defect.

VITAMIN B9 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin B9 is "necessary for the formation of normal red blood cells and the synthesis of DNA, the genetic material of cells." They also conclude that "Folic acid deficiency is common because many people do not eat enough raw leafy vegetables or citrus fruits." Given the very important nature of its functions, it seems wise to supplement with this nutrient.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B9 from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health.

FOLIC ACID EXCESS

Folic acid is generally not toxic. Very high doses may worsen nerve damage in people who have vitamin B12 deficiency.

VITAMIN B9 REFERENCES

1. Clarke R, Harrison G, Richards S; Vital Trial Collaborative Group. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. J Intern Med. 2003 Jul;254(1):67-75.

robert.clarke@ctsu.ox.ac.uk

OBJECTIVES: To examine the association of cognitive impairment with platelet activation and reactive oxygen species and total homocysteine levels; and to assess the biochemical efficacy of treatment with aspirin and vitamin supplements in people at high risk of dementia. SUBJECTS: People with dementia or mild cognitive impairment. DESIGN AND INTERVENTION: In a 2 x 2 x 2 factorial design trial, 149 people at high-risk of dementia were randomized to receive either low-dose aspirin (81 mg) or placebo; and folic acid (2 mg) plus vitamin B12 (1 mg) or placebo; and vitamins E (500 mg) plus C (200 mg) or placebo. Participants were seen twice before and once after 12 weeks of treatment. MAIN OUTCOME MEASURES: At each visit, participants had their cognitive function assessed and had blood collected for homocysteine, folate and vitamin B12 determination and urine collected for markers of platelet activation (11-dehydro-thromboxane B2) and reactive oxygen species (8-epi-PGF2 alpha). RESULTS: Prior to treatment, cognitive function was inversely related with homocysteine and with urinary thromboxane and isoprostane, and these associations were independent of age. Aspirin was associated with a median reduction in 11-dehydrothromboxane B2 of 73% ($P < 0.001$). B-vitamins lowered plasma homocysteine concentration by 30% ($P < 0.0001$) and antioxidant vitamins lowered isoprostane excretion by 26% ($P < 0.1$). No effect of treatment on cognitive function was detected. CONCLUSIONS: Aspirin and B-vitamins were effective in reducing biochemical factors associated with cognitive impairment in people at risk of dementia. Large-scale trials are now required to assess the relevance of aspirin and B-vitamins for the maintenance of cognitive function in people at risk of dementia.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 12823643 [PubMed - indexed for MEDLINE]

2. Duthie SJ, Whalley LJ, Collins AR, Leaper S, Berger K, Deary IJ. Homocysteine, B vitamin status, and cognitive function in the elderly. Am J Clin Nutr. 2002 May;75(5):908-13.

Erratum in:
* Am J Clin Nutr. 2003 Feb;77(2):523.

Comment in:
* Am J Clin Nutr. 2002 May;75(5):785-6.

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BACKGROUND: Old age is associated with reduced cognitive performance. Nutritional factors may contribute to this association. OBJECTIVE: We tested associations between cognitive performance and plasma vitamin B-12, folate, and homocysteine concentrations in the elderly. DESIGN: We studied survivors of the Scottish Mental Surveys of 1932 (Aberdeen 1921 Birth Cohort, or ABC21) and 1947 (Aberdeen 1936 Birth Cohort, or ABC36), which surveyed childhood intelligence quotient. We measured folate, vitamin B-12, and homocysteine concentrations in fasting blood samples and cognitive performance by the Mini Mental State Examination (MMSE), National Adult Reading Test (NART), Raven's Progressive Matrices (RPM), Auditory Verbal Learning Test (AVLT), digit symbol (DS) subtest, and block design (BD) subtest. RESULTS: Homocysteine was higher in the ABC21 than in the ABC36 ($P < 0.0001$). There were positive correlations between folate and vitamin B-12 and negative correlations between homocysteine and both folate and vitamin B-12. MMSE, RPM, AVLT, DS, and BD scores were higher in the ABC36. In the ABC21, folate, vitamin B-12, and MMSE score were positively correlated and homocysteine was negatively correlated with RPM, DS, and BD scores. Folic acid was positively correlated with AVLT and DS scores. In the ABC36, folate was positively correlated with BD score. After adjustment for childhood intelligence quotient, partial correlations were strengthened between vitamin B-12 and NART score and between homocysteine and RPM score but weakened between red blood cell folate and DS score. CONCLUSIONS: B vitamins and homocysteine are associated with cognitive variation in old age. In the ABC21 but not the ABC36, homocysteine accounted for approximately 7-8% of the variance in cognitive performance. This may prove relevant to the design of neuroprotective studies in late life.

PMID: 11976166 [PubMed - indexed for MEDLINE]

3. Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. J Neurol Neurosurg Psychiatry. 2000 Aug;69(2):228-32.

Comment in:
* J Neurol Neurosurg Psychiatry. 2001 Mar;70(3):419.

Department of Neurology, King's College Hospital, London, UK.

OBJECTIVES: Previous studies suggest that folate deficiency may occur in up to one third of patients with severe depression, and that treatment with the vitamin may enhance recovery of the mental state. There are, however, difficulties in interpreting serum and red cell folate assays in some patients, and it has been suggested that total plasma homocysteine is a more sensitive measure of functional

folate (and vitamin B12) deficiency. Other studies suggest a link between folate deficiency and impaired metabolism of serotonin, dopamine, and noradrenaline (norepinephrine), which have been implicated in mood disorders. A study of homocysteine, folate, and monoamine metabolism has, therefore, been undertaken in patients with severe depression. METHODS: In 46 inpatients with severe DSM III depression, blood counts, serum and red cell folate, serum vitamin B12, total plasma homocysteine, and, in 28 patients, CSF folate, S-adenosylmethionine, and the monoamine neurotransmitter metabolites 5HIAA, HVA, and MHPG were examined. Two control groups comprised 18 healthy volunteers and 20 patients with neurological disorders, the second group undergoing CSF examination for diagnostic purposes. RESULTS: Twenty four depressed patients (52%) had raised total plasma homocysteine. Depressed patients with raised total plasma homocysteine had significant lowering of serum, red cell, and CSF folate, CSF S-adenosylmethionine and all three CSF monoamine metabolites. Total plasma homocysteine was significantly negatively correlated with red cell folate in depressed patients, but not controls. CONCLUSIONS: Utilising total plasma homocysteine as a sensitive measure of functional folate deficiency, a biological subgroup of depression with folate deficiency, impaired methylation, and monoamine neurotransmitter metabolism has been identified. Detection of this subgroup, which will not be achieved by routine blood counts, is important in view of the potential benefit of vitamin replacement.

Publication Types:
* Clinical Trial
* Controlled Clinical Trial

PMID: 10896698 [PubMed - indexed for MEDL

4. Morris MS, Fava M, Jacques PF, Selhub J, Rosenberg IH. Depression and folate status in the US Population. Psychother Psychosom. 2003 Mar-Apr;72(2):80-7.

Comment on:
* Psychother Psychosom. 2003 Mar-Apr;72(2):59-60.

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BACKGROUND: Folate deficiency and low folate status have been linked in clinic studies to depression, persistent depressive symptoms, and poor antidepressant response. These relationships have not been demonstrated in general populations. This study examined associations between depression and folate status indicators in an ethnically diverse general US population sample aged 15-39 years. METHODS: Healthy subjects whose red blood cell (RBC) folate concentrations had been measured were determined to have no depression (n = 2,526), major depression (n = 301), or dysthymia (n = 121) using a diagnostic interview schedule. Serum concentrations of folate and total homocysteine (tHcy) were also measured. RESULTS: After adjustment for sociodemographic factors, serum vitamin B(12) concentration, alcohol consumption over the past year and current status as to overweight and use of vitamin/mineral supplements, cigarettes and illegal drugs, subjects who met criteria for a lifetime diagnosis of major depression had folate concentrations in serum and RBCs that were lower than those of subjects who had never been depressed. Subjects who met criteria for dysthymia alone had lower RBC folate concentrations than never-depressed subjects, but the serum folate

concentrations of the two groups were comparable. Serum tHcy concentration was not related to lifetime depression diagnoses. Low folate status was found to be most characteristic of recently recovered subjects, and a large proportion of such subjects were folate deficient. CONCLUSIONS: Low folate status was detectable in depressed members of the general US population. Folate supplementation may be indicated during the year following a depressive episode. Copyright 2003 S. Karger AG, Basel.

Publication Types:
* Comment

PMID: 12601225 [PubMed - indexed for MEDLINE]

5. Tolmunen T, Voutilainen S, Hintikka J, Rissanen T, Tanskanen A, Viinamaki H, Kaplan GA, Salonen JT. Dietary folate and depressive symptoms are associated in middle-aged Finnish men. J Nutr. 2003 Oct;133(10):3233-6W.

Department of Psychiatry, University of Kuopio, Finland.

Several cross-sectional studies have focused on the low blood folate levels of depressed patients. However, no published studies have examined the association between dietary folate and current symptoms of depression in a general population. We investigated the association between dietary folate, cobalamin, pyridoxine and riboflavin and current symptoms of depression in a cross-sectional general population study. We recruited 2682 men aged between 42 and 60 y from eastern Finland. Those who had a previous history of psychiatric disorder were excluded (n = 146, 5.6% of the cohort). Depressive symptoms were assessed with the 18-item Human Population Laboratory Depression Scale. Those who scored 5 or more at baseline were considered to have elevated depressive symptoms (n = 228, 9.3% of the cohort). The participants were grouped into thirds according to their dietary folate intake. Those in the lowest third of energy-adjusted folate intake had a higher risk of being depressed [odds ratio (OR) 1.67, 95% CI = 1.19-2.35, P = 0.003] than those in the highest folate intake third. This increased risk remained significant after adjustment for smoking habits, alcohol consumption, appetite, BMI, marital status, education, adulthood socioeconomic status and total fat consumption (OR = 1.46, 95% CI = 1.01-2.12, P = 0.044). There were no associations between the intake of cobalamin, pyridoxine or riboflavin, and depression. These results indicate that nutrition may have a role in the prevention of depression.

PMID: 14519816 [PubMed - indexed for MEDLINE]

VITAMIN B12

Research has demonstrated a link between vitamin B12 deficiency or imbalance and depression[1], dementia[2], cognitive function[3], and Alzheimer's[4].

The following description of Vitamin B12 is taken from *The Merck Manual Second Home Edition.*

Vitamin B12 (cobalamin), with folic acid, is necessary for the maturation of red blood cells and the synthesis of DNA (deoxyribonucleic acid), the genetic material of cells. Vitamin B12 is also necessary for normal nerve function. Unlike most other vitamins, B12 is stored in substantial amounts, mainly in the liver. The body's stores of this vitamin would take about 3 to 5 years to exhaust.

VITAMIN B12 DEFICIENCY

Usually, vitamin B12 deficiency is due to inadequate absorption. The cause may be lack of intrinsic factor, a protein produced in the stomach. Normally, vitamin B12 is readily absorbed in the last part of the small intestine (ileum), which leads to the large intestine. However, to be absorbed, the vitamin must combine with intrinsic factor. Without intrinsic factor, vitamin B12 remains in the intestine and is excreted in the stool. Intrinsic factor may be lacking because, for example, abnormal antibodies, produced by an overactive immune system, attack and destroy the stomach cells that produce intrinsic factor—an autoimmune reaction.

Older people may have a vitamin B12 deficiency because stomach acidity is low, reducing the body's ability to remove vitamin B12 from the protein in meat. Abnormal growth of bacteria in the small intestine may reduce the absorption of vitamin B12. Disorders that impair the absorption of nutrients in the intestine can reduce the absorption of vitamin B12. Fish tapeworm infection may also reduce the absorption of vitamin B12 in the intestine. Liver disorders may interfere with the storage of vitamin B12. Surgery that removes the stomach (where intrinsic factor is produced) or the part of the small intestine where vitamin B12 is absorbed can result in a deficiency. A strict vegetarian diet may also cause vitamin B12 deficiency because vitamin B12 is available only in animal products. Infants who are breastfed by a mother who is a strict vegetarian are at risk of vitamin B12 deficiency.

Symptoms

Because vitamin B12 is necessary for the production of mature blood cells, deficiency of this vitamin can result in anemia, characterized by abnormally large red blood cells (macrocytes) and white blood cells with abnormal nuclei. The type of anemia that results when an autoimmune reaction destroys the stomach cells that produce intrinsic factor is called pernicious anemia. Because the liver stores a large amount of vitamin B12, pernicious anemia may not develop until 3 to 5 years after the body stops absorbing vitamin B12.

Vitamin B12 deficiency anemia develops gradually, allowing the body to adapt somewhat. Consequently, the anemia may be more severe than the symptoms indicate. Anemia causes paleness, weakness, and fatigue. Severe anemia causes shortness of breath, dizziness, and a rapid heart rate.

Vitamin B12 deficiency can also cause nerve damage (neuropathy) even when no anemia develops, particularly in people older than 60. The legs are affected earlier

and more often than the arms. Tingling is felt in the feet and hands, and sensation in the legs, feet, and hands is lost. Vibration and position senses are also lost. Mild to moderate muscle weakness develops, and reflexes may be lost. Walking becomes difficult. Some people become confused, irritable, and mildly depressed. Advanced vitamin B12 deficiency may lead to delirium, paranoia, and impaired mental function, including dementia.

Diagnosis

Usually, vitamin B12 deficiency is suspected when routine blood tests detect large red blood cells. If this deficiency is suspected, the level of vitamin B12 in the blood is measured. If a deficiency is confirmed in an older person, no other tests are performed, because the cause, such as low stomach acidity, is usually not serious. In a younger person, tests to determine the cause may be performed, usually focusing on intrinsic factor.

If the cause of vitamin B12 deficiency is still unclear, a Schilling test may be performed. A tiny amount of radioactive vitamin B12 is given by mouth, and the amount absorbed is measured. Then vitamin B12 is given with intrinsic factor, and the amount absorbed is measured. If vitamin B12 is absorbed only when given with intrinsic factor, the diagnosis of pernicious anemia is confirmed.

Treatment

Treatment of vitamin B12 deficiency or pernicious anemia consists of replacing vitamin B12. People who have symptoms due to nerve damage are usually given vitamin B12 by injection. Injections, which may be self-administered, are given daily or weekly for several weeks until the level of vitamin B12 returns to normal. Then injections are given once a month indefinitely, unless the disorder causing it can be corrected. For people who have the deficiency but no symptoms, the vitamin may be taken by mouth or as a nasal gel, but blood tests are performed periodically to make sure the vitamin B12 level returns to and remains normal. Severe symptoms--for example, dementia in an older person--may not resolve.

VITAMIN B12 DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation Vitamin B12 is "is necessary for the maturation of red blood cells and the synthesis of DNA... Vitamin B12 is also necessary for normal nerve function". B12 deficiency is minimized by assuming that we get enough in our diet and that there are several years of B12 stored in the body.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of vitamin B12 from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

VITAMIN B12 REFERENCES

1. Tiemeier H, van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. Am J Psychiatry. 2002 Dec;159(12):2099-101.

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OBJECTIVE: The associations of vitamin B(12), folate, and homocysteine with depression were examined in a population-based study. METHOD: The authors screened 3,884 elderly people for depressive symptoms. Subjects with positive screening results had psychiatric workups. Folate, vitamin B(12), and homocysteine blood levels were compared in 278 persons with depressive symptoms, including 112 with depressive disorders, and 416 randomly selected reference subjects. Adjustments were made for age, gender, cardiovascular disease, and functional disability. RESULTS: Hyperhomocysteinemia, vitamin B(12) deficiency, and to a lesser extent, folate deficiency were all related to depressive disorders. For folate deficiency and hyperhomocysteinemia, the association with depressive disorders was substantially reduced after adjustment for functional disability and cardiovascular disease, but for vitamin B(12) this appeared independent. CONCLUSIONS: The association of vitamin B(12) and folate with depressive disorders may have different underlying mechanisms. Vitamin B(12) may be causally related to depression, whereas the relation with folate is due to physical comorbidity.

Publication Types:
* Clinical Trial

PMID: 12450964 [PubMed - indexed for MEDLINE]

2. Kessler H, Bleich S, Falkai P, Supprian T. Homocysteine and dementia. Fortschr Neurol Psychiatr. 2003 Mar;71(3):150-6.

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Homocysteine is a vascular risk factor including cerebral macroangiopathy and microangiopathy. Furthermore, there might also be an association with cognitive disorders including vascular dementia and Alzheimer's disease. Hyperhomocysteinemia linked with cognitive impairment might be an indirect marker for low concentrations of vitamin B 12, vitamin B 6 or folate, resulting from low intake or from an impaired transport of the vitamins to the brain. Another possibility is a direct harmful effect of homocysteine to cognition via vascular and neurotoxic pathophysiologic mechanisms. Because hyperhomocysteinemia is a potentially reversible risk factor and can be identified early, it should be investigated by prospective intervention studies whether lowering homocysteine levels by vitamin supplementation could reduce incidence and progression of cognitive disorders.

Publication Types:
* Review
* Review, Tutorial

PMID: 12624852 [PubMed - indexed for MEDLINE]

3. Nilsson K, Gustafson L, Hultberg B. Improvement of cognitive functions after cobalamin/folate supplementation in elderly patients with dementia and elevated plasma homocysteine. Int J Geriatr Psychiatry. 2001 Jun;16(6):609-14.

Department of Psychogeriatrics, Division of Psychiatry, University of Lund, University Hospital, Sweden. karin.nilsson@nc.lund. Itskane.se

OBJECTIVES: To investigate the effect of cobalamin/folate supplementation on cognitive function in elderly patients with dementia. METHOD: The cobalamin/folate status of the patients was evaluated by measuring plasma homocysteine, serum methylmalonic acid, serum cobalamin and blood folate. Thirty-three patients were studied and repeatedly assessed with the Mini-Mental State Examination (MMSE) and 'A short cognitive performance test for assessing memory and attention' (SKT) during vitamin substitution. RESULTS: Patients with mild-moderate dementia and elevated plasma homocysteine levels improved clinically with increased test scores after vitamin substitution, while severely demented patients and patients with normal plasma homocysteine levels did not improve clinically. CONCLUSIONS: Plasma homocysteine may be the best marker for detecting treatable cobalamin/folate deficiency in patients with dementia.

Publication Types:
* Clinical Trial

PMID: 11424170 [PubMed - indexed for MEDLINE]

4. Quadri P, Fragiacomo C, Pezzati R, Zanda E, Forloni G, Tettamanti M, Lucca U. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am J Clin Nutr. 2004 Jul;80(1):114-22.

Memory Clinic, Geriatric Division and Department of Metabolic Diseases, Ospedale Regionale della Beata Vergine, Mendrisio, Switzerland. pierluigi.quadri@bluewin.ch

BACKGROUND: Evidence supports an independent association between plasma total homocysteine concentrations and the risk of vascular disease. Recent epidemiologic studies reappraised the possibility that vascular risk factors might play a role in the pathogenesis not only of vascular dementia (VaD) but also of Alzheimer disease (AD). OBJECTIVE: The objective was to investigate the relations of mild cognitive impairment, AD, and VaD with blood homocysteine, folate, and vitamin B-12. DESIGN: The study population consisted of 314 consecutive subjects, 228 of whom were eligible for analyses. Plasma total homocysteine, serum folate, and serum vitamin B-12 concentrations were measured in 55 nondemented elderly control subjects, 81 mildly cognitively impaired subjects (Clinical Dementia Rating: 0.5), and 92 demented patients prevalently in a mild disease stage and with a clinical diagnosis of AD (n = 74) or VaD (n = 18). RESULTS: Subjects in the lowest folate tertile had significantly higher adjusted odds ratios (ORs) for mild cognitive impairment (OR: 3.1; 95% CI: 1.2, 8.1) and dementia (3.8; 1.3, 11.2). Hyperhomocysteinemia was significantly associated with dementia (adjusted OR: 4.3; 1.3, 14.7) and AD (adjusted OR: 3.7; 1.1, 13.1). In subjects with a Clinical Dementia Rating of 0.5, the mean (+/- SE) Mini-Mental State Examination score was significantly lower ($P < 0.05$) in the highest homocysteine tertile (24.5 +/- 0.5) than in the lowest tertile (26.6 +/- 0.5). No significant associations were found between minimum medial temporal lobe thickness or leukoaraiosis and any biochemical measure in the dementia and AD groups. CONCLUSIONS: These findings suggest that relative folate deficiency may precede AD and VaD onset. Hyperhomocysteinemia might also be an early

risk factor for cognitive decline in the elderly, but its role in dementia development must be addressed in future longitudinal studies.

PMID: 15213037 [PubMed - indexed for MEDLINE]

VITAMIN H (BIOTIN)

The following research demonstrates the importance of biotin in human health and disease[1,2,3] and regulation of gene expression[4], and in glucose balance[5].

The following description of biotin is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

BIOTIN DEFICIENCY AND DEPENDENCY

Biotin functions as a coenzyme for carbon dioxide transfer and hence is essential to fat and carbohydrate metabolism. A specific enzyme links biotin to its apoenzymes.

Deficiency: Raw egg white contains a biotin antagonist, avidin. Prolonged consumption of raw egg whites may result in dermatitis and glossitis, which respond rapidly to 150 to 300 μg biotin daily. Deficiency has also occurred during long-term TPN without supplementary biotin.

Dependency: Retarded physical and mental development, alopecia, keratoconjunctivitis, and defects in T-cell and B-cell immunity have been reported in children with deficiencies of multiple biotin-dependent carboxylases. Deficiencies result from mutations in holocarboxylase synthetase (the enzyme required to link biotin to four carboxylases necessary for metabolism) or in biotinidase (the enzyme required to remove biotin from the same enzymes in catabolism). Urinary excretion of various organic acids assists diagnosis. Children with holocarboxylase synthetase and biotinidase abnormalities respond well to large doses of biotin (5 to 20 mg) daily.

BIOTIN DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation biotin, which is part of the B vitamin complex, "is essential to fat and carbohydrate metabolism". Biotin deficiency results in "dermatitis and glossitis". And in the severe state of biotin dependency, "Retarded physical and mental development" may result. BENDER, 1999 states that "Biotin deficiency leads to impaired glucose tolerance."

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of biotin from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

BIOTIN REFERENCES

1. Pacheco-Alvarez D, Solorzano-Vargas RS, Del Rio AL. Biotin in metabolism and its relationship to human disease. Arch Med Res. 2002 Sep-Oct;33(5):439-47.

Departamento de Biologia Molecular y Biotecnologia, Instituto de Investigaciones Biomedicas (IIBM), Universidad Nacional Autonoma de Mexico (UNAM), Mexico City, Mexico.

Biotin, a water-soluble vitamin, is used as cofactor of enzymes involved in carboxylation reactions. In humans, there are five biotin-dependent carboxylases: propionyl-CoA carboxylase; methylcrotonyl-CoA carboxylase; pyruvate carboxylase, and two forms of acetyl-CoA carboxylase. These enzymes catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism; thus, biotin plays an essential role in maintaining metabolic homeostasis. In recent years, biotin has been associated with several diseases in humans. Some are related to enzyme deficiencies involved in biotin metabolism. However, not all biotin-responsive disorders can be explained based on the classical role of the vitamin in cell metabolism. Several groups have suggested that biotin may be involved in regulating transcription or protein expression of different proteins. Biotinylation of histones and triggering of transduction signaling cascades have been suggested as underlying mechanisms behind these non-classical biotin-deficiency manifestation in humans.

Publication Types:
* Review
* Review, Tutorial

PMID: 12459313 [PubMed - indexed for MEDLINE]

2. Rodriguez Melendez R. Importance of biotin metabolism. Rev Invest Clin. 2000 Mar-Apr;52(2):194-9.

Departamento de Medicina, Instituto de Investigaciones Biomedicas, UNAM, Mexico, D.F. rocior@servidor.unam.mx

Biotin is a water soluble enzyme cofactor that belongs to the vitamin B complex. In humans, biotin is involved in important metabolic pathways such as gluconeogenesis, fatty acid synthesis, and amino acid catabolism by acting a as prosthetic group for pyruvate carboxylase, propionyl-CoA carboxylase, beta-methylcrotinyl-CoA carboxylase, and acetyl-CoA carboxylase. Carboxylases are synthesized as apo-carboxylases without biotin and the active form is produced by their covalent binding of biotin to the epsilon-amino group of a lysine residue of the apocarboxylases. This reaction is catalyzed by the holo-carboxylase synthetase. The last step in the degradation of carboxylases, the cleavage of the biotinyl moiety from the epsilon-amino group lysine residues, is catalyzed by biotinidase and results in the release of free biotin, which can be recycled. Biotin regulates the catabolic enzyme propionyl-CoA carboxylase at the posttranscriptional level whereas the holo-carboxylase synthetase is regulated at the transcriptional level. Aside from its role in the regulation of gene expression of carboxylases, biotin has been implicated in the induction of the receptor for the asialoglycoprotein, glycolytic enzymes and of egg yolk biotin binding proteins. Biotin deficiency in humans is extremely rare and is generally associated with prolonged parenteral nutrition, the consumption of large quantities of avidin, usually in the form of raw eggs, severe malnutrition and, inherited metabolic disorders. In humans, there are autosomal recessive disorders of biotin metabolism that result from the disruption of the activity of biotinidase or holo-carboxylase synthetase.

Publication Types:
* Review
* Review, Tutorial

PMID: 10846444 [PubMed - indexed for MEDLINE]

3. Mock DM, Henrich CL, Carnell N, Mock NI. Indicators of marginal biotin deficiency and repletion in humans: validation of 3-hydroxyisovaleric acid excretion and a leucine challenge. Am J Clin Nutr. 2002 Nov;76(5):1061-8.

Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205, USA. mockdonaldm@uams.edu

BACKGROUND: The results of clinical studies have provided evidence that marginal biotin deficiency is more common than was previously thought. A previous study of 10 subjects showed that the urinary excretion of biotin and 3-hydroxyisovaleric acid (3HIA) are early and sensitive indicators of marginal biotin deficiency. OBJECTIVE: Marginal biotin deficiency was experimentally induced and corrected to assess the utility of 3 indicators of biotin status: urinary excretion of biotin and 3HIA and the increase in 3HIA excretion after leucine loading. DESIGN: Eleven healthy adults consumed an egg white diet for 28 d. Blood and 24-h urine samples were collected before the start of the diet and twice weekly thereafter. In 5 subjects, an oral leucine challenge was performed weekly for 4 wk. After depletion, biotin status was restored with a general diet with or without a supplement containing 80 micro g biotin. Urinary excretion of biotin, bisnorbiotin, and biotin sulfoxides was determined by avidin-binding assay after HPLC. Excretion of 3HIA, an indicator of reduced activity of the biotin-dependent enzyme methylcrotonyl-CoA carboxylase (EC 6.4.1.4), was measured by gas chromatography-mass spectrometry. RESULTS: 3HIA excretion increased significantly with time on the egg white diet ($P < 0.0001$), as did 3HIA excretion in response to the leucine challenge ($P < 0.002$); the excretion of both biotin and bisnorbiotin decreased significantly with time ($P < 0.0001$). In most subjects, biotin status returned to normal after 1 wk of a general diet. CONCLUSIONS: Excretion of 3HIA and of biotin are early and sensitive indicators of biotin deficiency. 3HIA excretion after a leucine challenge is at least as sensitive.

Publication Types:
* Validation Studies

PMID: 12399279 [PubMed - indexed for MEDLINE]

4. Rodriguez-Melendez R, Zempleni J. Regulation of gene expression by biotin (review). J Nutr Biochem. 2003 Dec;14(12):680-90.

Department of Nutritional Science and Dietetics, University of Nebraska at Lincoln, NE 68583, USA

In mammals, biotin serves as coenzyme for four carboxylases, which play essential roles in the metabolism of glucose, amino acids, and fatty acids. Biotin deficiency causes decreased rates of cell proliferation, impaired immune function, and abnormal fetal development. Evidence is accumulating that biotin also plays an important role in regulating gene expression, mediating some of the effects of biotin in cell biology and fetal development. DNA microarray studies and other gene expression studies have suggested that biotin affects transcription of genes encoding cytokines and their receptors, oncogenes, genes involved in glucose metabolism, and genes that play a role in cellular biotin homeostasis. In addition, evidence has been provided that biotin affects expression of the asialoglycoprotein receptor and propionyl-CoA carboxylase at the post-transcriptional level. Various pathways have been identified by which biotin might affect gene expression: activation of soluble guanylate cyclase by biotinyl-AMP, nuclear translocation of

NF-kappaB (in response to biotin deficiency), and remodeling of chromatin by biotinylation of histones. Some biotin metabolites that cannot serve as coenzymes for carboxylases can mimic biotin with regard to its effects on gene expression. This observation suggests that biotin metabolites that have been considered "metabolic waste" in previous studies might have biotin-like activities. These new insights into biotin-dependent gene expression are likely to lead to a better understanding of roles for biotin in cell biology and fetal development.

Publication Types:
* Review
* Review, Tutorial

PMID: 14690760 [PubMed - indexed for MEDLINE]

5. Bender DA. Optimum nutrition: thiamin, biotin and pantothenate. Proc Nutr Soc. 1999 May;58(2):427-33. "Biotin deficiency leads to impaired glucose tolerance."

Department of Biochemistry and Molecular Biology, University College London, UK. dab@biochem.ucl.ac.uk

The metabolism of glucose is deranged in thiamin deficiency, but once any deficiency has been corrected there is no further effect of increased thiamin intake on the ability to metabolize glucose through either pyruvate dehydrogenase (EC 1.2.4.1) and the citric acid cycle, or the pentose phosphate pathway, in which transketolase (EC 2.2.1.1) is the thiamin-dependent step. It has been suggested that the Wernicke-Korsakoff syndrome is associated with a genetic variant of transketolase which requires a higher than normal concentration of thiamin diphosphate for activity. This finding would suggest that there may be a group of the population who have a higher than average requirement for thiamin, but the evidence is not convincing. There are no estimates of biotin requirements, but either coenzyme saturation of erythrocyte pyruvate carboxylase, or the excretion of 3-hydroxy-isovalerate (perhaps after a test dose of leucine) could be used to assess requirements in depletion-repletion studies. Biotin deficiency leads to impaired glucose tolerance, but it is unlikely that glucose tolerance could be used to assess optimum biotin status, since other more common factors affect glucose tolerance to a greater extent. Plasma triacylglycerol and nonesterified fatty acids are moderately elevated in pantothenic acid deficiency. However, this is unlikely to be useful in assessing pantothenate status, since again, other more common factors affect plasma lipids. To date there are no biochemical indices of adequate pantothenate nutrition, and no estimates of requirements.

Publication Types:
* Review
* Review, Tutorial

PMID: 10466187 [PubMed - indexed for MEDLINE]

CALCIUM

Research has demonstrated a link between calcium deficiency or imbalance and premenstrual syndrome symptoms of anxiety and tension[1,2,3,4].

The following description of calcium is taken from *The Merck Manual Second Home Edition.*

Most of the body's calcium is stored in the bones, but calcium is also found in cells (particularly muscle cells) and in the blood. Calcium is essential to muscle contraction and to the normal functioning of many enzymes. It is necessary for the formation of bone and teeth, for blood clotting, and for normal heart rhythm.

The body precisely controls the amount of calcium in the cells and the blood. Maintaining a normal level of calcium in the blood depends on consuming at least 1,000 to 1,500 milligrams of calcium a day and excreting excess calcium in urine. Calcium moves out of the bones into the bloodstream as needed to maintain a steady level of calcium in the blood. However, mobilizing too much calcium from the bones weakens them and can lead to osteoporosis.

The level of calcium in the blood is regulated primarily by two hormones: parathyroid hormone and calcitonin. Parathyroid hormone is produced by the four parathyroid glands, located around the thyroid gland in the neck. When the calcium level in the blood falls, the parathyroid glands produce more parathyroid hormone. When the calcium level in the blood rises, the parathyroid glands produce less hormone. Parathyroid hormone stimulates the digestive tract to absorb more calcium and causes the kidneys to activate vitamin D. Vitamin D further enhances the ability of the digestive tract to absorb calcium. Parathyroid hormone also stimulates the bones to release calcium into the blood and causes the kidneys to excrete less calcium in urine. Calcitonin, a hormone produced by cells of the thyroid gland, lowers the calcium level in the blood by slowing the breakdown of bone.

HYPOCALCEMIA

In hypocalcemia, the level of calcium in the blood is too low. Most of the calcium in the blood is carried by (bound to) the protein albumin. Albumin-bound calcium acts as a reserve but has no active function in the body. By contrast, unbound (ionized) calcium affects the body's functions. Thus, a low level of albumin in the blood usually causes no problems as long as the amount of unbound calcium remains normal. The total calcium level in the blood usually parallels the level of unbound calcium.

Hypocalcemia is most commonly caused by excessive calcium loss in the urine or a failure to move calcium out of the bones into the bloodstream. Hypocalcemia may result when the level of parathyroid hormone is low (for example, if the parathyroid glands are damaged during thyroid gland surgery), when a person is born without parathyroid glands, or when the body responds poorly to a normal level of parathyroid hormone (pseudohypoparathyroidism). A low level of magnesium may cause hypocalcemia by reducing the activity of parathyroid hormone. Other causes of hypocalcemia include vitamin D deficiency (due to poor nutrition or inadequate exposure to sunlight), kidney damage (which increases loss of calcium in urine and reduces the kidneys' ability to activate vitamin D), inadequate intake of calcium in the diet, disorders that affect calcium absorption, and pancreatitis.

The calcium level in the blood can be moderately low without producing any symptoms. Over time, hypocalcemia can affect the brain and cause neurologic or psychologic symptoms, such as confusion, memory loss, delirium, depression, and hallucinations. These symptoms are reversible if the calcium level is restored. An extremely low calcium level may cause tingling (often in the lips, tongue, fingers, and feet), muscle aches, spasms of the muscles in the throat (leading to difficulty breathing), stiffening and spasms of muscles (tetany), and abnormal heart rhythms.

Hypocalcemia is often detected by routine blood tests before symptoms become obvious.

Oral calcium supplements are often all that is needed to treat hypocalcemia. Once symptoms appear, intravenous administration of calcium is usually warranted. Taking vitamin D supplements helps increase the absorption of calcium from the digestive tract.

CALCIUM DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation calcium is not just a structural mineral. "Calcium is essential to muscle contraction and to the normal functioning of many enzymes. It is necessary for the formation of bone and teeth, for blood clotting, and for normal heart rhythm." However, most of the emphasis on calcium is placed on its structural abilities, and that is done to the exclusion of other minerals, such as magnesium, that are crucial for both calcium absorption and its proper utilization.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack calcium from lack of essential nutrients found in fresh whole foods, which leads to a host of health problems.

HYPERCALCEMIA

In hypercalcemia, the level of calcium in the blood is too high. Hypercalcemia is commonly caused by hyperparathyroidism (the excessive secretion of parathyroid hormone by one or more of the four parathyroid glands).

Another cause of hypercalcemia is the ingestion of large amounts of calcium. Occasionally, hypercalcemia develops in people with peptic ulcers if they drink a lot of milk and take calcium-containing antacids for relief. The resulting disorder is called the milk-alkali syndrome. An overdose of vitamin D can also affect the calcium level in the blood by greatly increasing the absorption of calcium from the digestive tract.

Hypercalcemia often occurs in people who have cancer. Cancers of the kidneys, lungs, and ovaries may secrete large amounts of a protein that has effects similar to those of parathyroid hormone. These effects are considered a paraneoplastic syndrome (see Section 15, Chapter 181). Calcium can also be released into the blood when cancer spreads (metastasizes) to bone and destroys bone cells. Such bone destruction occurs most commonly with cancers of the prostate, breast, and lung. Multiple myeloma (a cancer involving bone marrow) can also lead to the

destruction of bone and result in hypercalcemia. Other cancers can raise the calcium level in the blood by means not yet fully understood.

Hypercalcemia often produces no symptoms. The earliest symptoms are usually constipation, nausea, vomiting, abdominal pain, loss of appetite, and abnormally large amounts of urine. Very severe hypercalcemia often causes brain dysfunction with confusion, emotional disturbances, delirium, hallucinations, and coma. Muscle weakness may occur, and abnormal heart rhythms and death can follow. Kidney stones containing calcium may form in people with chronic hypercalcemia.

Hypercalcemia is usually discovered during routine blood tests.

If the hypercalcemia is not severe, correcting the cause is often sufficient. People who have normal kidney function and a tendency to develop hypercalcemia are usually advised to drink plenty of fluids, which stimulates the kidneys to excrete calcium and helps prevent dehydration.

CALCIUM REFERENCES

1. Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. Am J Obstet Gynecol. 1998 Aug;179(2):444-52.

Summary for patients in:
* Can Fam Physician. 2002 Apr;48:705-7.

St. Luke's-Roosevelt Hospital Center, College of Physicians and Surgeons, Columbia University, New York, New York 10019, USA.

OBJECTIVE: Previous reports have suggested that disturbances in calcium regulation may underlie the pathophysiologic characteristics of premenstrual syndrome and that calcium supplementation may be an effective therapeutic approach. To evaluate the effect of calcium carbonate on the luteal and menstrual phases of the menstrual cycle in premenstrual syndrome, a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial was conducted. STUDY DESIGN: Healthy, premenopausal women between the ages of 18 and 45 years were recruited nationally across the United States at 12 outpatient centers and screened for moderate-to-severe, cyclically recurring premenstrual symptoms. Symptoms were prospectively documented over 2 menstrual cycles with a daily rating scale that had 17 core symptoms and 4 symptom factors (negative affect, water retention, food cravings, and pain). Participants were randomly assigned to receive 1200 mg of elemental calcium per day in the form of calcium carbonate or placebo for 3 menstrual cycles. Routine chemistry, complete blood cell count, and urinalysis were obtained on all participants. Daily documentation of symptoms, adverse effects, and compliance with medications were monitored. The primary outcome measure was the 17-parameter symptom complex score. RESULTS: Seven hundred twenty women were screened for this trial; 497 women were enrolled; 466 were valid for the efficacy analysis. There was no difference in age, weight, height, use of oral contraceptives, or menstrual cycle length between treatment groups. There were no differences between groups in the mean screening symptom complex score of the luteal (P = .659), menstrual (P = .818), or intermenstrual phase (P = .726) of the menstrual cycle. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was

observed in the calcium-treated group for both the second (P = .007) and third (P < .001) treatment cycles. By the third treatment cycle calcium effectively resulted in an overall 48% reduction in total symptom scores from baseline compared with a 30% reduction in placebo. All 4 symptom factors were significantly reduced by the third treatment cycle. CONCLUSIONS: Calcium supplementation is a simple and effective treatment in premenstrual syndrome, resulting in a major reduction in overall luteal phase symptoms.

Publication Types:
* Clinical Trial
* Multicenter Study
* Randomized Controlled Trial

PMID: 9731851 [PubMed - indexed for MEDLINE]

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PMID: 12138870 [PubMed]

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Metabolic Bone Center, St. Luke's-Roosevelt Hospital Center, College of Physicians and Surgeons, Columbia University, New York, New York 10019, USA.

Premenstrual syndrome afflicts millions of premenopausal women and has been described as one of the most common disorders in women. Research over the past few years suggests that a variety of nutrients may have an important role in the phase related mood and behavioral disturbances of the premenstrual syndrome. There is scientific evidence, at least for a few of these micronutrients, specifically calcium and vitamin D, supporting cyclic fluctuations during the menstrual cycle that may help explain some features of PMS. Ovarian hormones influence calcium, magnesium and vitamin D metabolism. Estrogen regulates calcium metabolism, intestinal calcium absorption and parathyroid gene expression and secretion, triggering fluctuations across the menstrual cycle. Alterations in calcium homeostasis (hypocalcemia and hypercalcemia) have long been associated with many affective disturbances. PMS shares many features of depression, anxiety and the dysphoric states. The similarity between the symptoms of PMS and hypocalcemia is remarkable. Clinical trials in women with PMS have found that calcium supplementation effectively alleviates the majority of mood and somatic symptoms. Evidence to date indicates that women with luteal phase symptomatology have an underlying calcium dysregulation with a secondary hyperparathyroidism and vitamin D deficiency. This strongly suggests that PMS represents the clinical manifestation of a calcium deficiency state that is unmasked following the rise of ovarian steroid hormone concentrations during the menstrual cycle.

Publication Types:
* Review
* Review, Tutorial

PMID: 10763903 [PubMed - indexed for MEDLINE]

4. Ward MW, Holimon TD. Calcium treatment for premenstrual syndrome. Ann Pharmacother. 1999 Dec;33(12):1356-8.

College of Pharmacy, University of Tennessee, Memphis 38163, USA.

OBJECTIVE: To evaluate the use of calcium supplementation in the treatment of premenstrual syndrome. DATA SOURCES: Clinical literature accessed through MEDLINE (from January 1967 to September 1999). Key search terms included calcium, PMS, and premenstrual. DATA SYNTHESIS: Up to 50% of women experience some form of premenstrual syndrome. An evaluation of studies focusing on calcium in the management of premenstrual symptoms was conducted. CONCLUSIONS: Calcium supplementation of 1200-1600 mg/d, unless contraindicated, should be considered a sound treatment option in women who experience premenstrual syndrome. The supplemental dose of calcium can be adjusted downward in the few patients who routinely consume large quantities of calcium in their diet.

Publication Types:
* Review
* Review, Tutorial

PMID: 10630835 [PubMed - indexed for MEDLINE]

PHOSPHORUS

Research has shown an influence of phosphorus deficiency or imbalance on anxiety[1,2,3] and ADHD[4,5] symptoms.

The following description of phosphorus is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

PHOSPHATE METABOLISM

Phosphorus is one of the most abundant elements in the human body. Most phosphorus in the body is complexed with oxygen as phosphate (PO4). About 85% of the roughly 500 to 700 g of PO4 in the body is contained in bone, where it is an important constituent of the crystal hydroxyapatite. In soft tissues, PO4 is mainly found in the intracellular compartment. It is an integral component of several organic compounds, including nucleic acids and the phospholipids of cell membranes. PO4 is also intimately involved in aerobic and anaerobic energy metabolism. RBC 2,3-diphosphoglycerate (2,3-DPG) plays a crucial role in O2 delivery to tissue. Inorganic PO4 is a major intracellular anion, but it is also present in plasma. The normal plasma inorganic PO4 concentration in adults ranges from 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L). PO4 is up to 50% higher in infants and 30% higher in children, possibly because of higher phosphate requirements for growth.

The typical American diet contains about 800 to 1500 mg of PO4. This amount appears in the stool in varying amounts depending on the amount of PO4 binding compounds (mainly Ca) in the diet. Like Ca, gastrointestinal PO4 absorption is also enhanced by vitamin D. Renal PO4 excretion roughly equals GI absorption to maintain net PO4 balance. PO4 depletion can occur in a variety of disease states and results in conservation of PO4 by the kidneys. Bone PO4 serves as a reservoir, which can buffer changes in plasma and intracellular PO4.

DISORDERS OF PHOSPHATE METABOLISM

HYPOPHOSPHATEMIA

A decrease in plasma phosphate concentration below 2.5 mg/dL (0.81 mmol/L).

Incidence, Etiology, and Pathogenesis

Hypophosphatemia is seen in 2% of hospitalized patients, but is more prevalent in certain populations, eg, alcoholics, in whom it is seen in up to 10% of hospitalized patients. Common clinical settings of acute severe hypophosphatemia include the recovery phase of diabetic ketoacidosis, acute alcoholism, and severe burns. Hypophosphatemia may also occur in patients receiving total parenteral nutrition and in severe chronic respiratory alkalosis.

Hypophosphatemia has numerous causes, but clinically significant hypophosphatemia occurs in relatively few settings. **Chronic hypophosphatemia** most often results from a fall in renal PO4 reabsorption and is not associated with intracellular PO4 depletion. Causes include hyperparathyroidism; other hormonal disturbances, such as Cushing's syndrome and hypothyroidism; electrolyte disorders, such as hypomagnesemia and hypokalemia; theophylline intoxication; and chronic diuretic administration. **Severe chronic hypophosphatemia** usually results from a prolonged negative PO4 balance. Causes include chronic starvation

or malabsorption, especially if combined with vomiting or copious diarrhea or chronic ingestion of large amounts of PO4-binding aluminum, usually in the form of antacids. The latter is particularly prone to produce PO4 depletion when combined with decreased dietary intake and dialysis losses of PO4 in patients with end-stage renal disease.

Acute hypophosphatemia with plasma phosphorus < 1 mg/dL (< 0.32 mmol/L) is most often caused by transcellular shifts of PO4, often superimposed on chronic hypophosphatemia and PO4 depletion.

Symptoms, Signs, and Diagnosis

Although hypophosphatemia usually is asymptomatic, anorexia, muscle weakness, and osteomalacia can occur in severe chronic depletion. Serious neuromuscular disturbances may occur, including progressive encephalopathy, coma, and death. The muscle weakness of profound hypophosphatemia may be accompanied by rhabdomyolysis, especially in acute alcoholism. Hematologic disturbances of profound hypophosphatemia include hemolytic anemia, decreased release of O2 from hemoglobin, and impaired leukocyte and platelet function.

HYPERPHOSPHATEMIA

An increase in plasma phosphate concentration above 4.5 mg/dL (1.46 mmol/L).

Incidence, Etiology, and Pathogenesis

Hyperphosphatemia generally results from a decrease in renal excretion of PO4. Advanced renal insufficiency (GFR < 20 mL/ min) results in sufficient reduction in excretion to lead to increases in plasma PO4. Defects in the renal excretion of PO4 in the absence of renal failure also occur in pseudohypoparathyroidism and hypoparathyroidism. Hyperphosphatemia can also be seen with excessive oral PO4 administration and occasionally with the overzealous use of phosphate-containing enemas.

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MAGNESIUM

Magnesium: Research has demonstrated a link between magnesium deficiency or imbalance and premenstrual syndrome[1,2,3], depression[4], aging[5], and ADHD[6].

The following description of magnesium is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

MAGNESIUM METABOLISM

Magnesium (Mg) is the fourth most plentiful cation in the body. A 70-kg adult has roughly 2000 mEq of Mg. About 50% is sequestered in bone and is not readily exchangeable with other compartments. The ECF contains only about 1% of total body Mg. The remainder resides in the intracellular compartment. Normal plasma Mg concentration ranges from 1.4 to 2.1 mEq/L (0.70 to 1.05 mmol/L).

The maintenance of plasma Mg concentration is largely a function of dietary intake and extremely effective renal and intestinal conservation. Within 7 days of initiation of a Mg-deficient diet, renal and fecal Mg excretion each fall to about 1 mEq/24 h (0.5 mmol/24 h).

About 70% of plasma Mg is ultrafiltered by the kidney; the remainder is bound to protein. As with Ca, protein binding of Mg is pH dependent. Plasma Mg concentration and either total body Mg or intracellular Mg content are not closely related. However, severe plasma hypomagnesemia may reflect diminished body stores of Mg.

A wide variety of enzymes are Mg activated or dependent. Mg is required by all enzymatic processes involving ATP and is also required by many of the enzymes involved in nucleic acid metabolism. Mg is required for thiamine pyrophosphate cofactor activity and appears to stabilize the structure of macromolecules such as DNA and RNA. Mg is also related to Ca and K metabolism in an intimate but poorly understood way.

DISORDERS OF MAGNESIUM METABOLISM

HYPOMAGNESEMIA

Plasma magnesium concentration below 1.4 mEq/L (0.70 mmol/L).

Severe hypomagnesemia often is equated with Mg depletion. However, plasma Mg concentration, even if free Mg ion is measured, may not reflect the status of intracellular or bone Mg stores.

The disorders associated with Mg deficiency are complex and usually accompanied by multiple metabolic and nutritional disturbances.

ETIOLOGY AND PATHOGENESIS

Mg depletion usually results from inadequate intake plus impairment of renal or gut absorption. It has been described in association with prolonged parenteral feeding, usually in combination with loss of body fluids via gastric suction or diarrhea; lactation (increased requirement for Mg); and conditions of abnormal renal conservation of Mg, such as hypersecretion of aldosterone, ADH, or thyroid hormone; hypercalcemia; diabetic acidosis; and cisplatin or diuretic therapy.

Clinically significant Mg deficiency most commonly is associated with (1) malabsorption syndromes from all causes, in which elevated fecal Mg is probably related to the level of steatorrhea rather than to deficient bowel absorptive sites per se; (2) protein-calorie malnutrition (eg, kwashiorkor); (3) parathyroid disease, in which hypomagnesemia occurs after removal of a parathyroid tumor, especially if severe osteitis fibrosa is present (presumably, Mg is transferred to rapidly mineralizing bone, and Mg deficiency may account for the resistance of hypocalcemia to correction with vitamin D in occasional patients with hypoparathyroidism); (4) chronic alcoholism, in which hypomagnesemia probably is due to both inadequate intake and excessive renal excretion; and (5) chronic diarrhea.

Symptoms and Signs

On the basis of experimental Mg depletion in human volunteers, the clinical manifestations of Mg deficiency are anorexia, nausea, vomiting, lethargy, weakness, personality change, tetany (eg, positive Trousseau's or Chvostek's sign or spontaneous carpopedal spasm), and tremor and muscle fasciculations. The neurologic signs, particularly tetany, correlate with the development of concomitant hypocalcemia and hypokalemia. Myopathic potentials are found on electromyography but are also compatible with hypocalcemia or hypokalemia. Although not observed experimentally, it is likely that severe hypomagnesemia may produce generalized tonic-clonic seizures, especially in children.

Laboratory Findings

Hypomagnesemia is often present when Mg depletion is severe. Hypocalcemia and hypocalciuria are common in patients with steatorrhea, alcoholism, or other causes of Mg deficiency. Hypokalemia with increased urinary K excretion and metabolic alkalosis may be present. Thus, unexplained hypocalcemia and hypokalemia should suggest the possibility of Mg depletion.

Treatment

Treatment with Mg salts (sulfate or chloride) is indicated when Mg deficiency is symptomatic or associated with severe, persistent hypomagnesemia < 1 mEq/L (< 0.5 mmol/L). In such cases, deficits approaching 12 to 24 mg/kg are possible. About twice the amount of the estimated deficit should be given in patients with intact renal function, since about 50% of the administered Mg will be excreted in the urine. Usually, half of the dose is given in the first 24 h and the remainder over the next 4 days. Parenteral administration is reserved for patients who have severe, symptomatic hypomagnesemia or who are unable to tolerate oral drugs. When Mg must be replaced parenterally, a 10% magnesium sulfate (MgSO4) solution (1 g/10 mL) is available for IV use, and a 50% (1 g/2 mL) solution is used for IM use. The plasma Mg level should be monitored frequently during Mg therapy, particularly when Mg is given parenterally or to patients with renal insufficiency. Treatment is continued until a normal plasma Mg level is achieved.

In severe, symptomatic hypomagnesemia (eg, generalized seizures, Mg < 1 mEq/L [< 0.5 mmol/L]), 2 to 4 g of MgSO4 may be given IV over 5 to 10 min. If seizures persist, the dose may be repeated up to a total of 10 g over the next 6 h. If seizures stop, 10 g in 1 L of 5% D/W can be infused over 24 h, followed by up to 2.5 g q 12 h to replace the deficit in total Mg stores and prevent further drops in plasma Mg. When plasma Mg is < 1 mEq/L (< 0.5 mmol/L) but symptoms are less severe, $MgSO_4$ may be given IV in 5% D/W at a rate of 1 g/h as slow infusion for up to 10

h. In less severe cases of hypomagnesemia, gradual repletion may be achieved by administration of smaller parenteral doses over 3 to 5 days until the plasma Mg level is normal. (See also use of $MgSO_4$ under Preeclampsia and Eclampsia in Ch. 252.)

Hypocalcemic patients who are also Mg-depleted with resulting hypomagnesemia generally require Mg repletion in addition to Ca administration.

MAGNESIUM DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation magnesium deficiency symptoms include "anorexia, nausea, vomiting, lethargy, weakness, personality change, tetany and tremor and muscle fasciculations. Some of these symptoms can be interpreted as anxiety and stress reactions for which magnesium is the treatment.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of magnesium from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

DRUG INTERACTIONS MERCK

High levels of aldosterone, antidiuretic hormone, or thyroid hormones can cause hypomagnesemia by increasing the excretion of magnesium by the kidneys. Diuretics, the antifungal drug amphotericin B, or the chemotherapy drug cisplatin can also cause hypomagnesemia.

HYPERMAGNESEMIA

Plasma magnesium concentration above 2.1 mEq/L (1.05 mmol/L).

Symptomatic hypermagnesemia is fairly uncommon, but when it does occur it usually does so in patients with renal failure after ingestion of Mg-containing drugs such as antacids or purgatives.

MAGNESIUM REFERENCES

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Department of Food Science and Technology, The University of Reading, United Kingdom.

To investigate single and combined effects of daily dietary supplementation with 50 mg of vitamin B6 and 200 mg magnesium (as MgO) for one cycle for the relief of mild premenstrual symptoms, a randomized, double-blind, placebo-controlled, crossover design was used. Forty-four women with an average age of 32 years took part in the study. Each woman was randomly assigned, according to a Latin square design, to take consecutively all four of the following treatments daily for one

menstrual cycle: (1) 200 mg Mg, (2) 50 mg vitamin B6, (3) 200 mg Mg + 50 mg vitamin B6 and (4) placebo. Throughout the study, each volunteer kept a daily record of symptoms using a 5-point ordinal scale in a menstrual diary of 30 symptoms. Symptoms were grouped into six categories: anxiety, craving, depression, hydration, other, and total. Urinary magnesium output for 24 hours was estimated using the Mg/creatinine concentration ratio. ANOVA showed no overall difference between individual treatments, but predefined treatment comparisons using factorial contrasts in ANOVA showed a significant effect of 200 mg/day Mg + 50 mg/day vitamin B6 on reducing anxiety-related premenstrual symptoms (nervous tension, mood swings, irritability, or anxiety) ($p = 0.040$). Urinary Mg output was not affected by treatment. A small synergistic effect of a daily dietary supplementation with a combination of Mg + vitamin B6 in the reduction of mild premenstrual anxiety-related symptoms was demonstrated during treatment of 44 women for one menstrual cycle. In view of the modest effect found, further studies are needed before making general recommendations for the treatment of premenstrual symptoms. The study indicated that absorption from MgO was poor and daily supplementation for longer than 1 month is necessary for tissue repletion.

Publication Types:
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* Randomized Controlled Trial
PMID: 10746516 [PubMed - indexed for MEDLINE]

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Hugh Sinclair Unit of Human Nutrition, Department of Food Science and Technology, University of Reading, U.K.

We investigated the effect of a daily supplement of 200 mg of magnesium (as MgO) for two menstrual cycles on the severity of premenstrual symptoms in a randomized, double-blind, placebo-controlled, crossover study. A daily supplement of 200 mg of Mg (as MgO) or placebo was administered for two menstrual cycles to each volunteer, who kept a daily record of her symptoms, using a 4-point scale in a menstrual diary of 22 items. Symptoms were grouped into six categories: PMS-A (anxiety), PMS-C (craving), PMS-D (depression), PMS-H (hydration), PMS-O (other), and PMS-T (total overall symptoms). Urinary Mg output/24 hours was estimated from spot samples using the Mg/creatinine ratio. Analysis of variance for 38 women showed no effect of Mg supplementation compared with placebo in any category in the first month of supplementation. In the second month there was a greater reduction ($p = 0.009$) of symptoms of PMS-H (weight gain, swelling of extremities, breast tenderness, abdominal bloating) with Mg supplementation compared with placebo. Compliance to supplementation was confirmed by the greater mean estimated 24-hour urinary output of Mg ($p = 0.013$) during Mg supplementation (100.8 mg) compared with placebo (74.1 mg). A daily supplement of 200 mg of Mg (as MgO) reduced mild premenstrual symptoms of fluid retention in the second cycle of administration.

Publication Types:
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* Randomized Controlled Trial

PMID: 9861593 [PubMed - indexed for MEDLINE]

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Geha Psychiatric Hospital, Felsenstein Medical Research Center, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel.

BACKGROUND: Minor depression is reported in 20-60% of schizophrenic patients during various stages of their disorders; impairing patients' compliance, response to treatment and worsening their overall prognosis. Various anti-depressive treatments have been proposed for such cases but response rates are usually poor. Pyridoxine (Vitamin B6) in essential for the proper metabolism of various neurotransmitters that are considered relevant to the pathophysiology of depression and/or schizophrenia and it has been reported beneficial in ameliorating depressive symptoms as part of major depression, premenstrual syndrome or 'Chinese restaurant syndrome'. We hypothesized that addition of pyridoxine to on-going neuroleptic treatment could improve minor depression in schizophrenic patients. METHOD: Nine schizophrenic patients with co-morbid minor depression participated in this study. All participants had a stable unchanged clinical state (changes in Brief Psychiatric Rating Scale (BPRS). Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative symptoms (SANS) scores < 5%) and all were maintained on unchanged doses of anti-psychotic drugs for at least 4 consecutive weeks prior to initiation of the study. Participants received, open-label, pyridoxine 150 mg/day in addition to their anti-psychotic treatment for 4 consecutive weeks. Mental status was evaluated before, during, and at the end of 4 weeks of pyridoxine administration using the BPRS, SAPS, SANS and HAM-D. RESULTS: Two of the nine patients (22%), characterized by higher initial HAM-D and SANS scores, and by older age and longer duration of illness, experienced marked improvements in depressive symptoms (23% and 28% decrease in HAM-D scores) following 4 weeks of pyridoxine administration. In one of these two, the improvement in depressive symptoms was accompanied by a parallel decrease in SANS Scores. CONCLUSION: A subgroup of schizophrenic patients with comorbid minor depression may benefit from pyridoxine addition to their on-going anti-psychotic treatment.

Publication Types:
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* Multicenter Study

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Centre of Nutrition, Medical Hospital and Research Centre, Moradabad, India.

This cross-sectional survey was conducted in 20 randomly selected streets in Moradbad city in North India to determine the association of magnesium and antioxidant vitamins with risk of ageing. There were 595 subjects (314 males, 281 females) between 50-84 years of age inclusive. The overall prevalence of hypomagnesemia was 11.8 per cent (n = 60) with a prevalence of 13.2 per cent (n = 33) in males and 10.6 per cent (n = 27) in females. The prevalence of hypomagnesemia showed significant declining trend in the concentration of serum magnesium, vitamin C, vitamin E and beta-carotene and a rising trend in lipid peroxides and diene conjugates with increase in age from 50-59 years to 70-84 years in both men and women. Multivariate logistic regression analysis showed that serum magnesium, vitamin C, vitamin E and beta-carotene were significant risk factors of ageing in both men and women. The findings suggest that some urban populations of India can benefit by consuming higher dietary magnesium, potassium and antioxidant vitamins for prevention of ageing.

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[Article in Polish]

Oddzialu Psychiatrii Dzieci, Dzieckiem i Mlodzieza w Szczecinie.

The aim of my work was the answer to the following questions: how often does the deficiency of magnesium, copper, zinc, calcium, iron occur among hyperactive children in comparison with healthy children, deficiency of which of the considered bioelements is the most frequent, what is the effect of supplementation of deficit element on hyperactivity and does it depend on other certain disorders that coexist with hyperactivity? In a process of establishing the subject diagnosis I have followed the DSM IV criteria recognizing ADHD among examined ones. I have determined the deficiency of magnesium, copper, zinc, calcium, iron in the group of 116 children with diagnosed ADHD. Consequently, as a result, I have found out that shortage of above-mentioned bioelements occurs more often among hyperactive children than among those being healthy, and deficiency of magnesium is the most frequent in this respect. Further, I have divided the group of 110 children with magnesium deficiency into two groups according to the other mental disorders that coexist with ADHD: 1) the group where hyperactivity coexists with disorders typical for developmental age such as enuresis, tics, separation anxiety, stuttering, selective mutism (63 children); 2) the group where hyperactivity coexists with disruptive behaviour disorders: conduct disorder and oppositional defiant disorder (47 children). The content of magnesium, copper, zinc, calcium, iron has been determined respectively in blood (serum and red cells) and in hair by atomic absorption spectroscopy method in both groups accordingly. At the same time, the hyperactivity tests were carried out using Conner's Rating Scales for Parents and Teachers, Wender's Scale as well as Quotient of Development to Freedom from Distractibility. During the statistical analysis the inparametric tests have been used taking as a significance level $p < 0.05$. On the ground of obtained findings I have not stated any significant differences in bioelements content among hyperactive children in relation to other coexisting disorders, except for zinc. The zinc content in hair was higher among children with ADHD and disruptive behaviour disorder. The assessment of hyperactivity indicated the remarkably higher coefficient among

children with coexisting behaviour disorders as compared to hyperactive children among whom, additionally, disorders typical for developmental age have occurred. The analysis of influence exerted by magnesium supplementation on hyperactivity has been carried out in the group of total 75 children with ADHD jointly with magnesium deficiency. The group of 50 children actually tested, apart from standard treatment have received the specified doses of magnesium preparations for 6 months on regular basis. The group of 25 children was left with standard treatment without additional magnesium. In both above-mentioned groups the content of bioelements and respectively ADHD level have been determined just before and after the test. The obtained results have clearly disclosed significant increase of magnesium, zinc, calcium content (Tab. 1) and respectively essential decrease of hyperactivity in the group of children treated with magnesium. At the same time, however, among the children given standard treatment without magnesium, hyperactivity has intensified (Tab. 3, 4). The findings herein presented indicate that it is necessary to take into consideration a possible bioelements deficiency among children with ADHD. Consequently, the accomplished study proves that there is a need of magnesium supplementation in ADHD children irrespectively of other mental disorders. The supplementation of that kind of magnesium supplementation together with standard traditional mode of treatment gives us the opportunity to extend the methods of therapy of ADHD children who are the "children of the risk" in connection with their educational, emotional and social problems.

PMID: 9857546 [PubMed - indexed for MEDLINE]

POTASSIUM

Studies have demonstrated a link between potassium deficiency or imbalance and aggression[1,2,3], anxiety[4], bipolar disorder[5,6,7,8], and depression[1,9].

The following description of potassium is taken from *The Merck Manual Second Home Edition.*

Most of the body's potassium is located inside the cells. Potassium is necessary for the normal functioning of cells, nerves, and muscles.

The level of potassium in the blood must be maintained within a narrow range. A potassium level that is too high or too low can have serious consequences, such as an abnormal heart rhythm or even cardiac arrest. The potassium stored within the cells can be used by the body to help maintain a constant level of potassium in the blood.

Potassium balance is achieved by matching the amount of potassium taken in with the amount lost. Potassium is taken in through food and electrolyte-containing drinks and lost primarily in urine, although some potassium is also lost through the digestive tract and in sweat. Healthy kidneys are able to adjust the excretion of potassium to match changes in dietary intake. Some drugs and certain conditions affect the movement of potassium into and out of cells, which greatly influences the potassium level in the blood.

HYPOKALEMIA

In hypokalemia, the level of potassium in the blood is too low. Excessive potassium loss usually results from vomiting, diarrhea, chronic laxative use, or colon polyps. Very occasionally, excessive loss results from excessive sweating in conditions of extreme heat and humidity. Many foods contain potassium, so hypokalemia is rarely caused by too little intake in people who eat a balanced diet.

There are several reasons why potassium may be lost in the urine. By far the most common is the use of diuretics that cause the kidneys to excrete excess sodium, water, and potassium. In Cushing's syndrome, the adrenal glands produce excess amounts of aldosterone, a hormone that causes the kidneys to excrete large amounts of potassium (see Section 13, Chapter 164). Excessive potassium is also excreted by people who eat large amounts of licorice or chew certain types of tobacco.

Certain drugs (such as insulin and the antiasthmatic drugs albuterol, terbutaline, and theophylline) increase the movement of potassium into the cells and can result in hypokalemia. However, use of these drugs is rarely the sole cause of hypokalemia.

A mild decrease in the potassium level in the blood usually causes no symptoms. A more severe decrease can cause muscle weakness, twitches, and even paralysis. Abnormal heart rhythms may develop, especially in people with heart disease. Even mild hypokalemia is dangerous in people taking the heart drug digoxin. The diagnosis is made by determining that the potassium level in the blood is low.

Potassium usually can be replaced by eating potassium-rich foods or by taking potassium supplements by mouth. Because potassium can irritate the digestive tract, supplements should be taken in small doses with food several times a day

rather than in a single large dose. Special types of potassium supplements, such as wax-impregnated or microencapsulated potassium chloride, are much less likely to irritate the digestive tract.

Most people who take diuretics do not need to take potassium supplements. Nevertheless, doctors periodically check the potassium level in the blood so that the drug regimen can be altered if necessary. Alternatively, potassium-conserving diuretics (such as triamterene, amiloride, or spironolactone) can be added to the diuretic therapy, but only in people whose kidneys are functioning normally.

POTASSIUM DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "Potassium is necessary for the normal functioning of cells, nerves, and muscles." And "The level of potassium in the blood must be maintained within a narrow range." The citation minimizes the most common cause of potassium deficiency, which is due to the use of diuretics.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of potassium from lack of essential nutrients found in fresh fruits, vegetables, which leads to a host of health problems.

HYPERKALEMIA

In hyperkalemia, the level of potassium in the blood is too high. Hyperkalemia usually results when the kidneys do not excrete enough potassium. Probably the most common cause of mild hyperkalemia is the use of drugs that decrease blood flow to the kidneys or prevent the kidneys from excreting normal amounts of potassium. Such drugs include triamterene, spironolactone, and angiotensin-converting enzyme (ACE) inhibitors. Hyperkalemia can also be caused by Addison's disease, in which the adrenal glands do not produce sufficient amounts of the hormone aldosterone, which stimulates the kidneys to excrete potassium (see Section 13, Chapter 164). Kidney failure can result in severe hyperkalemia.

Hyperkalemia can also result when a large amount of potassium is suddenly released from the cells. A sudden release of potassium from the cells can result from crush injuries (involving the destruction of large amounts of muscle tissue), severe burns, or overdoses of crack cocaine. The rapid movement of potassium from the cells into the bloodstream can overwhelm the kidneys and result in life-threatening hyperkalemia.

Mild hyperkalemia causes few, if any, symptoms. Usually, hyperkalemia is first detected when routine blood tests are performed or when a doctor notices changes on an electrocardiogram. A high level of potassium in the blood is dangerous. It can cause the heart rhythm to become abnormal. If the level is very high, the heart can stop beating.

For mild hyperkalemia, reducing the potassium intake or discontinuing drugs that prevent the kidneys from excreting potassium may be the only treatment that is

needed. If the kidneys are functioning, a diuretic may be given to increase potassium excretion.

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IODINE (FROM PACIFIC KELP)

Research has demonstrated a world-wide deficiency in iodine[1,2,3,4], deficiency in pregnancy[5], as well as its requirement in thyroid function[6].

The primary function of iodine (I) in the body is to provide a substrate for the synthesis of the thyroid hormones, thyroxine and triiodothyronine, which are crucial for normal growth and development. The thyroid gland, which weighs 15 to 20 g, contains 80% of the body's iodine pool--about 15 mg in adults. Iodide, the ionic form of iodine, is rapidly absorbed from the GI tract and distributed to extracellular water. Fasting plasma concentrations of iodide are about 1 μg/L (7.88 nmol/L). In adults, about 80% of the iodide ingested and absorbed is trapped by the thyroid gland through an ATP-dependent iodide pump (see Synthesis and Release of Thyroid Hormones in Ch. 8).

Iodide occurs in soil and seawater and is oxidized by sunlight to iodine, which is vaporized into the air. The iodide concentration is 50 to 60 μg/L (394 to 473 nmol/L) in seawater and 0.7 μg/m3 (5.51 nmol/L) in the air. Some of this iodide is returned to the soil by rain, but much is lost in the stratosphere. These events account for the continued depletion of iodine in soil, its lack of capture by plants, and continuing iodine deficiency in humans, particularly at higher altitudes in countries where salt is not fortified with iodide. In iodine-deficient areas, the iodide concentration in drinking water is < 2 μg/L (< 15.8 nmol/L), whereas in areas close to the sea, the drinking water contains 4 to 10 μg/L (31.5 to 78.8 nmol/L). The usual intake of iodide in healthy persons is 100 to 200 μg/day, mostly from iodized salt (70 μg/g).

IODINE DEFICIENCY

Iodine deficiency results when iodide intake is < 20 μg/day. In moderate iodine deficiency, the thyroid gland, under the influence of thyroid-stimulating hormone, hypertrophies to concentrate iodide in itself, resulting in a colloid goiter. Most of these cases remain euthyroid.

Severe iodine deficiency may result in endemic myxedema among adults and in endemic cretinism among infants. Several metabolic disturbances in thyroid hormone synthesis can cause both adult and infantile hypothyroidism. But worldwide, endemic iodine deficiency is still a major cause of hypothyroidism. Severe maternal iodine deficiency retards fetal growth and brain development. Endemic cretinism may occur in one of two forms (neurologic or myxedematous), depending on the interplay of iodine deficiency and genetics.

Infants with iodine deficiency are given L-thyroxine (3 μg/kg/day) for a week plus 50 μg of iodide to quickly restore a euthyroid state. Iodide supplementation is continued. Plasma thyroid-stimulating hormone levels are monitored until they are in the normal range, ie, < 5 μIU/mL. Deficient adults are given iodide at a dose of 1500 μg/day--about 10 times the recommended daily allowance--for several weeks to restore the iodine content of the depleted gland and permit thyroxine synthesis.

Toxicity: Chronic iodine toxicity results when iodide intake is 20 times greater than the daily requirement, ie, 2 mg/day. In some areas, particularly Japan, inhabitants consume as much as 50 to 80 mg/day, resulting in high plasma levels. Some of these persons develop goiters, but most remain euthyroid. Some develop

myxedema, and some paradoxically develop hyperthyroidism (Jod-Basedow phenomenon). Increased uptake of iodine by the thyroid may lead to inhibition of thyroid hormone synthesis (Wolff-Chaikoff effect) and eventually causes iodide goiter or myxedema. At very high doses of iodide, a brassy taste, increased salivation, gastric irritation, and acneiform skin lesions may occur.

IODINE DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "The primary function of iodine (I) in the body is to provide a substrate for the synthesis of the thyroid hormones…, which are crucial for normal growth and development".

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of iodine from lack of essential nutrients found in fish and sea vegetables, which leads to a host of health problems.

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BACKGROUND: Maternal subclinical hypothyroidism is a cause of poor neurodevelopment outcome in the offspring. Although iodine deficiency is the most common cause of hypothyroidism world wide, there are no screening programmes for it in the United Kingdom where the population is assumed to be iodine replete. OBJECTIVE: To determine the prevalence of reduced iodine intake by measuring urinary iodide concentrations in pregnant and non-pregnant women from the north east of England. METHODS: Urinary iodide excretion (UIE) rate was estimated using inductively coupled mass spectrometry in 227 women at 15 weeks gestation and in 227 non-pregnant age matched controls. A reduced intake of iodine is indicated by a concentration in urine of less than 50 microg/l or less than 0.05 microg iodine/mmol creatinine. RESULTS: Eight (3.5%) pregnant women and 13 (5.7%) controls had a reduced iodine/creatinine ratio. These values were higher when UIE was expressed as iodine concentration: 16 (7%) and 20 (8.8%) respectively. Ninety (40%) of the pregnant women had a UIE of 0.05-0.10, which is consistent with borderline deficiency. CONCLUSION: In this study, 3.5% of pregnant women had evidence of iodine deficiency, and 40% may be borderline deficient. Larger scale studies are required to estimate the true prevalence of iodine deficiency in the United Kingdom.

PMID: 15321965 [PubMed - in process]

2. Zimmermann M, Delange F. Iodine supplementation of pregnant women in Europe: a review and recommendations. Eur J Clin Nutr. 2004 Jul;58(7):979-84.

Laboratory for Human Nutrition, Institute of Food Science and Nutrition, Swiss Federal Institute of Technology, Ruschlikon, Zurich, Switzerland. michael.zimmermann@ilw.agrl.ethz.ch

OBJECTIVE: Nearly two-thirds of the population of Western and Central Europe live in countries that are iodine deficient. Damage to reproductive function and to the development of the fetus and newborn is the most important consequence of iodine deficiency. The objective of this review was to examine the iodine status of pregnant women in Europe and the potential need for iodine supplementation. DESIGN: A MEDLINE/PubMed search and compilation of all published studies since 1990 of iodine nutrition and iodine supplementation of pregnant women in Europe, as well as an Internet-based search and review on availability and legislation of iodine supplements in the European Union. RESULTS: Although the data suggest most women in Europe are iodine deficient during pregnancy, less than 50% receive supplementation with iodine. Mild-to-moderate iodine deficiency during pregnancy adversely affects thyroid function of the mother and newborn and mental development of the offspring and these adverse effects can be prevented or minimized by supplementation. There are no published data on the effect of iodine supplementation on long-term maternal and child outcomes. The iodine content of prenatal supplements in Europe varies widely; many commonly used products contain no iodine. The European Union is developing legislation to establish permissible levels for iodine in food supplements. CONCLUSIONS: In most European countries, pregnant women and women planning a pregnancy should receive an iodine-containing supplement (approximately 150 microg/day). Kelp and seaweed-based products, because of unacceptable variability in their iodine content, should be avoided. Prenatal supplement manufacturers should be encouraged to include adequate iodine in their products. Professional organizations should influence evolving EU legislation to ensure optimal doses for iodine in prenatal vitamin-mineral supplements. SPONSORSHIP: International Council for Control of Iodine Deficiency Disorders.

PMID: 15220938 [PubMed - in process]

3. Glinoer D. The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. Best Pract Res Clin Endocrinol Metab. 2004 Jun;18(2):133-52.

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The main change in thyroid function associated with the pregnant state is the requirement of an increased production of thyroid hormone that depends directly upon the adequate availability of dietary iodine and integrity of the glandular machinery. Physiologic adaptation takes place when the iodine intake is adequate, while this is replaced by pathologic alterations when there is a deficient iodine intake. Pregnancy acts typically, therefore, as a revelator of underlying iodine restriction. Iodine deficiency (ID) has important repercussions for both the mother and the fetus, leading to sustained glandular stimulation, hypothyroxinemia and goitrogenesis. Furthermore, because severe ID may be associated with an impairment in the psycho-neuro-intellectual outcome in the progeny-because both mother and offspring are exposed to ID during gestation (and the postnatal period), and because ID is still prevalent today in several European countries-it has been

proposed already in the early 1990s that iodine supplements be given systematically to pregnant and breast-feeding women. Particular attention is required to ensure that pregnant women receive an adequate iodine supply, by administering multivitamin tablets containing iodine supplements, in order to achieve the ideal recommended dietary allowance of 200-250 microg iodine/day.

PMID: 15157832 [PubMed - in process]

4. Hollowell JG, Staehling NW, Hannon WH, Flanders DW, Gunter EW, Maberly GF, Braverman LE, Pino S, Miller DT, Garbe PL, DeLozier DM, Jackson RJ. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). J Clin Endocrinol Metab. 1998 Oct;83(10):3401-8.

Comment in:
* J Clin Endocrinol Metab. 1998 Oct;83(10):3398-400.

Centers for Disease Control, National Center for Environmental Health, Division of Environmental Hazards and Health Effects, Atlanta, Georgia 30341, USA. jgh1@cdc.gov

Iodine deficiency in a population causes increased prevalence of goiter and, more importantly, may increase the risk for intellectual deficiency in that population. The National Health and Nutrition Examination Surveys [NHANES I (1971-1974) and (NHANES III (1988-1994)] measured urinary iodine (UI) concentrations. UI concentrations are an indicator of the adequacy of iodine intake for a population. The median UI concentrations in iodine-sufficient populations should be greater than 10 microg/dL, and no more than 20% of the population should have UI concentrations less than 5 microg/dL. Median UI concentrations from both NHANES I and NHANES III indicate adequate iodine intake for the overall U.S. population, but the median concentration decreased more than 50% between 1971-1974 (32.0+/-0.6 microg/dL) and 1988-1994 (14.5+/-0.3 microg/dL). Low UI concentrations (<5 microg/dL) were found in 11.7% of the 1988-1994 population, a 4.5-fold increase over the proportion in the 1971-1974 population. The percentage of people excreting low concentrations of iodine (UI, <5 microg/dL) increased in all age groups. In pregnant women, 6.7%, and in women of child-bearing age, 14.9% had UI concentrations below 5 microg/dL. The findings in 1988-1994, although not indicative of iodine deficiency in the overall U.S. population, define a trend that must be monitored.

PMID: 9768638 [PubMed - indexed for MEDLINE]

5. Hamrosi MA, Wallace EM, Riley MD. Iodine status in early pregnancy: ethnic variations. Asia Pac J Clin Nutr. 2003;12 Suppl:S15.

Nutrition and Dietetics Unit, Monash University, VIC 3168.

Background - Iodine deficiency is re-emerging as a potential public health problem in Australia. Poor iodine status in pregnancy is associated with impaired fetal development, both mental and physical. Furthermore, there may be significant ethnic variation in maternal iodine status. Objective - To describe maternal iodine status in a multiethnic Australian population. Design - Cross-sectional. Urinary iodine (UI) concentration was measured in spot urine samples, collected in early

pregnancy, from Vietnamese, Indian/Sri Lankan and Caucasian women who participated in a Downs Syndrome Screening Program over 1999-2001 in Melbourne. Outcomes - WHO Iodine Status: Caucasian (n=178): 49.0 UImicrog/L (Median); 50.6 (%UI below 50micro/L); moderate iodine deficiency. Vietnamese (n=200): 56.5(1); UImicrog/L (Median); 38.5 (%UI below 50micro/L); mild iodine deficiency; Indian/Sri Lankan (n=181): 53.0(2) UImicrog/L (Median); 47.0 (%UI below 50micro/L); mild iodine deficiency. P=0.003 cf Caucasian; (2);P=0.15 cf Caucasian). Conclusions - Consistent with recent studies in non-pregnant individuals, these women were mildly to moderately iodine deficient according to World Health Organisation (WHO) criteria. The findings may have implications for fetal development and for public health advice.

PMID: 15023606 [PubMed - in process]

6. Bellisola G, Bratter P, Cinque G, Francia G, Galassini S, Gawlik D, Negretti de Bratter VE, Azzolina L. The TSH-dependent variation of the essential elements iodine, selenium and zinc within human thyroid tissues. J Trace Elem Med Biol. 1998 Nov;12(3):177-82.

Istituto di Immunologia e Malattie Infettive, Universita di Verona, Policlinico Borgo Roma, Italy.

Instrumental Neutron Activation Analysis was used in order to measure iodine, selenium and zinc concentration in thyroid samples. A pair of samples of normal and nodular tissue were collected from the thyroid gland from 72 patients selected on the basis of pathological criteria (44 cases of multinodular goiter, 12 of chronic lymphocytic thyroiditis (CLT), 6 of thyroid adenoma (TA) and 12 of thyroid cancer (TC)). The check for tissue homogeneity and sampling error was performed by means of the coefficient of variation (CV%) of the elements in replicate samples of normal and altered tissues. High CV% values (> 15%) for iodine reflected a functional variability in thyroid follicles, while low CV% values (< 10%) for selenium and zinc indicated that the composition of selected tissues was rather homogeneous. The variation of the element's concentration was compared in normal and altered tissues. The mean element concentrations had values close to those already reported in the literature; furthermore, our patients had marginal iodine and selenium deficiency. Both normal and nodular tissues in CLT showed statistically significant lower zinc values as compared with the other thyroid diseases. To evaluate the thyroid function, thyroid stimulating hormone (TSH) and thyroxine (T4) levels were measured in the serum of patients. Two arbitrary serum-TSH threshold levels (TSH < 1.0 and > 4.0 mU/L) were introduced in order to classify, respectively, hyperthyroidism and hypothyroidism, as well as euthyroid conditions (1.0 < TSH < 4.0 mU/L), and each patient was assigned to one of these groups. The influence of TSH in the variation of the concentration of iodine, selenium and zinc in normal and altered human thyroid tissues was significant.

PMID: 9857330 [PubMed - indexed for MEDLINE]

ZINC

Research has demonstrated a deficiency of zinc in the population[1,2] and a link between zinc deficiency or imbalance and schizophrenia[3], mitochondrial aging[4], DNA production[5], and thyroid function[6].

The following description of zinc is taken from *The Merck Manual Second Home Edition.*

Zinc is widely distributed in the body. It is a component of more than 100 enzymes, including those involved in the formation of RNA (ribonucleic acid) and DNA (deoxyribonucleic acid). The level of zinc in the body depends on the amount of zinc consumed in the diet. Zinc is necessary for healthy skin, healing of wounds, and growth. Much of the zinc consumed in the diet is not absorbed.

ZINC DEFICIENCY

Zinc deficiency is most likely to develop in people who eat little meat, liver, eggs, or seafood. Consuming phytic acid (found in grains) and large amounts of iron and calcium may reduce the absorption of zinc. Liver and pancreatic disorders, alcoholism, diabetes mellitus, and disorders that impair absorption can cause zinc deficiency. Taking diuretics can also cause zinc deficiency. People who must be fed intravenously for a long time may develop this deficiency. Acrodermatitis enteropathica, a rare hereditary disorder in which zinc cannot be absorbed, may result in zinc deficiency as well as diarrhea and rashes.

Early symptoms include a loss of appetite and slowed growth in infants and children. Other symptoms include patchy hair loss, impaired taste and smell, inflammation of the skin (dermatitis), and night blindness. In men, sperm production may be reduced. The body's immune system and ability to heal wounds may be impaired. In acrodermatitis enteropathica, symptoms usually appear when an affected infant is weaned.

Doctors suspect zinc deficiency on the basis of the person's circumstances, symptoms, and response to zinc supplements.

ZINC DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation, zinc "is a component of more than 100 enzymes, including those involved in the formation of RNA (ribonucleic acid) and DNA (deoxyribonucleic acid)." It is also "necessary for healthy skin, healing of wounds, and growth." You need to consume zinc from your diet but only about 20% is absorbed.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of zinc from lack of essential nutrients found in fresh whole foods, which leads to a host of health problems.

ZINC EXCESS

Consumption of excess zinc is rare. It usually results from consuming acidic foods or beverages packaged in a zinc-coated (galvanized) container. Symptoms include a metallic taste in the mouth, nausea, vomiting, and diarrhea. Consumption of 1 gram or more (about 70 times the RDA) may be fatal. In certain industries, inhaling zinc oxide fumes can cause rapid breathing, sweating, and weakness—a disorder called metal fume fever. Consuming too much zinc for a long time can reduce the absorption of copper and impair the immune system.

Doctors suspect the diagnosis based on the person's circumstances and symptoms. Treatment involves reducing zinc consumption.

ZINC REFERENCES

1. Ganji V, Hampl JS, Betts NM. Race-, gender- and age-specific differences in dietary micronutrient intakes of US children. Int J Food Sci Nutr. 2003 Nov;54(6):485-90.

Department of Consumer and Family Studies/Dietetics, San Francisco State University, San Francisco, CA 94132, USA. vijay@sfsu.edu

Race-, gender- and age-specific differences in dietary micronutrient intakes of 1- to 10-year-old US children were evaluated. Three-day, dietary intakes from the US Department of Agriculture's Continuing Survey of Food Intakes by Individuals were evaluated. Data from 1895 children (967 males, 928 females; 1,540 Whites, 355 Blacks) who resided in the 48 conterminous states were analyzed. Micronutrient intakes, intakes as percent of the Recommended Dietary Allowance (RDA) and percent of children who consumed < or =67% of the RDA were computed. Black males compared with White males, Black females compared with White females and White females compared with White males had significantly lower dietary intakes for several micronutrients. More Black males than White males had intakes < or =67% of the RDA for vitamin E, calcium and zinc. Blacks and female children were at a greater risk for vitamin A, vitamin E, calcium, iron and zinc deficiency.

PMID: 14522694 [PubMed - indexed for MEDLINE]

2. Oken E, Duggan C. Update on micronutrients: iron and zinc. Curr Opin Pediatr. 2002 Jun;14(3):350-3.

Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.

The past few years have seen several substantial advances in our understanding of the importance of micronutrients in child health and nutrition. Although historically child nutrition in developing countries has focused on protein and energy sufficiency, more recent efforts have been made to evaluate and eliminate micronutrient deficiencies. Accumulating data have underlined the important long-term health effects that may occur with iron deficiency, and studies continue to confirm the benefits of successful treatment of iron deficiency anemia. Zinc is another micronutrient whose significance to child health is increasingly appreciated. Although breakthroughs in micronutrient research have generally come from populations in developing countries, children in industrialized countries also benefit from increasing knowledge about nutritional requirements and interventions.

Publication Types:
* Review
* Review, Tutorial

PMID: 12011679 [PubMed - indexed for MEDLINE]

3. Pfeiffer CC & LaMola S. Zinc and manganese in the schizophrenics. J. Orthomol. Psychiatry 12: 215-234; 1983.

4. Atamna H. Heme, iron, and the mitochondrial decay of ageing. Ageing Res Rev. 2004 Jul;3(3):303-1.

Children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr. Way, Oakland, CA 94609-1673, USA. hatamna@chori.org

Heme, the major functional form of iron, is synthesized in the mitochondria. Although disturbed heme metabolism causes mitochondrial decay, oxidative stress, and iron accumulation, all of which are hallmarks of ageing, heme has been little studied in nutritional deficiency, in ageing, or age-related disorders such as Alzheimer's disease (AD). Biosynthesis of heme requires Vitamin B(6), riboflavin, biotin, pantothenic acid, and lipoic acid and the minerals zinc, iron, and copper. micronutrients are essential for the production of succinyl-CoA, the precursor for porphyrins, by the TCA (Krebs) cycle. Only a small fraction of the porphyrins synthesized from succinyl-CoA are converted to heme, the rest are excreted out of the body together with the degradation products of heme (e.g. bilirubin). Therefore, the heme biosynthetic pathway causes a net loss of succinyl-CoA from the TCA cycle. The mitochondrial pool of succinyl-CoA may limit heme biosynthesis in deficiencies for micronutrients (e.g. iron or biotin deficiency). Ageing and AD are also associated with hypometabolism, increase in heme oxygenase-1, loss of complex IV, and iron accumulation. Heme is a common denominator for all these changes, suggesting that heme metabolism maybe altered in age-related disorders. Heme can also be a prooxidant: it converts less reactive oxidants to highly reactive free radicals. Free heme has high affinity for different cell structures (protein, membranes, and DNA), triggering site-directed oxidative damage. This review discusses heme metabolism as related to metabolic changes seen in ageing and age-related disorders and highlights the possible role in iron deficiency.

PMID: 15231238 [PubMed - in process]

5. Ames BN. The metabolic tune-up: metabolic harmony and disease prevention. J Nutr. 2003 May;133(5 Suppl 1):1544S-8S. University of California, Berkeley and Children's Hospital, Oakland, CA 94609, USA.

University of California, Berkeley and Children's Hospital, Oakland, CA 94609, USA. bames@chori.org

An optimum intake of micronutrients and metabolites, which varies with age and genetic constitution, would tune up metabolism and give a marked increase in health, particularly for the poor and elderly, at little cost. 1) DNA damage. Inadequate intake of folic acid causes millions of uracils to be incorporated into the DNA of each cell with associated chromosome breaks, essentially producing a radiation mimic. Deficiencies of the metabolically connected vitamins B-6 and B-12, which are also widespread, also cause uracil incorporation and chromosome breaks. Inadequate iron intake (2 billion women in the world; 25% of U.S. menstruating

women) causes oxidants to leak from mitochondria and damages mitochondria and mitochondrial DNA. Inadequate zinc intake (approximately 10% in the U.S.) causes oxidation and DNA damage in human cells. 2) The K(m) concept. Approximately 50 different human genetic diseases that are due to a poorer binding affinity (K(m)) of the mutant enzyme for its coenzyme can be remedied by feeding high-dose B vitamins, which raise levels of the corresponding coenzyme. Many polymorphisms also result in a lowered affinity of enzyme for coenzyme. 3) Mitochondrial oxidative decay with age. This decay, which is a major contributor to aging, can be ameliorated by feeding old rats the normal mitochondrial metabolites acetyl carnitine and lipoic acid at high levels. They restore the K(m) for acetyl carnitine transferase and the velocity of the reaction as well as mitochondrial function; reduce levels of oxidants, neuron RNA oxidation and mutagenic aldehydes; and increase old-rat ambulatory activity and cognition.

Publication Types:
* Lectures

PMID: 12730462 [PubMed - indexed for MEDLINE]

6. Bellisola G, Bratter P, Cinque G, Francia G, Galassini S, Gawlik D, Negretti de Bratter VE, Azzolina L. The TSH-dependent variation of the essential elements iodine, selenium and zinc within human thyroid tissues. J Trace Elem Med Biol. 1998 Nov;12(3):177-82.

Istituto di Immunologia e Malattie Infettive, Universita di Verona, Policlinico Borgo Roma, Italy.

Instrumental Neutron Activation Analysis was used in order to measure iodine, selenium and zinc concentration in thyroid samples. A pair of samples of normal and nodular tissue were collected from the thyroid gland from 72 patients selected on the basis of pathological criteria (44 cases of multinodular goiter, 12 of chronic lymphocytic thyroiditis (CLT), 6 of thyroid adenoma (TA) and 12 of thyroid cancer (TC)). The check for tissue homogeneity and sampling error was performed by means of the coefficient of variation (CV%) of the elements in replicate samples of normal and altered tissues. High CV% values (> 15%) for iodine reflected a functional variability in thyroid follicles, while low CV% values (< 10%) for selenium and zinc indicated that the composition of selected tissues was rather homogeneous. The variation of the element's concentration was compared in normal and altered tissues. The mean element concentrations had values close to those already reported in the literature; furthermore, our patients had marginal iodine and selenium deficiency. Both normal and nodular tissues in CLT showed statistically significant lower zinc values as compared with the other thyroid diseases. To evaluate the thyroid function, thyroid stimulating hormone (TSH) and thyroxine (T4) levels were measured in the serum of patients. Two arbitrary serum-TSH threshold levels (TSH < 1.0 and > 4.0 mU/L) were introduced in order to classify, respectively, hyperthyroidism and hypothyroidism, as well as euthyroid conditions (1.0 < TSH < 4.0 mU/L), and each patient was assigned to one of these groups. The influence of TSH in the variation of the concentration of iodine, selenium and zinc in normal and altered human thyroid tissues was significant.

PMID: 9857330 [PubMed - indexed for MEDLINE]

SELENIUM

Research has demonstrated a link between selenium deficiency or imbalance and brain disease[1], brain function[2], antioxidant status[3], environmental detoxification[4], and environment stressors[5].

The following description of selenium is taken from *The Merck Manual Second Home Edition.*

Selenium occurs in all tissues. Selenium works with vitamin E as an antioxidant. It helps protect cells against damage by free radicals, which are reactive by-products of normal cell activity. Selenium is also necessary for the thyroid gland to function normally.

SELENIUM DEFICIENCY

Selenium deficiency is rare, even in New Zealand and Finland, where selenium intake is much lower than in the United States and Canada. In China, where selenium intake is even lower, selenium deficiency occurs in association with Keshan disease, a viral disease that affects mainly children and young women. Keshan disease damages the heart, resulting in cardiomyopathy.

In selenium deficiency, antioxidants are lacking in the heart and muscles. As a result, cardiomyopathy and muscle weakness may occur.

Doctors suspect selenium deficiency on the basis of the person's circumstances and symptoms. Treatment with a selenium supplement may result in a complete recovery.

SELENIUM DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "Selenium works with vitamin E as an antioxidant. It helps protect cells against damage by free radicals, which are reactive by-products of normal cell activity. Selenium is also necessary for the thyroid gland to function normally." The Merck Manual also states that "selenium deficiency is rare". We also note that the focus on selenium deficiency is on the severe instance of Keshan's disease. There is no mention of mild selenium deficiency or any reference to subclinical selenium deficiency. Because selenium, as with other minerals, must come form the soil and be absorbed by plants, if there is an agricultural area that has been depleted of selenium, then selenium is not found in our food

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of selenium from lack of essential nutrients found in the soil and found in fresh whole foods, which leads to a host of health problems.

SELENIUM EXCESS

Taking more than 1 milligram of a nonprescription selenium supplement each day can have harmful effects. Symptoms include nausea and vomiting, loss of hair and nails, a skin rash, and nerve damage. The diagnosis is based on symptoms, particularly rapid hair loss. Treatment involves reducing selenium consumption. (The amount of selenium needed in the body is measured in micrograms.)

SELENIUM REFERENCES

1. Chen J, Berry MJ. Selenium and selenoproteins in the brain and brain diseases. J Neurochem. 2003 Jul;86(1):1-12.

Department of Cell and Molecular Biology, University of Hawaii at Manoa, Honolulu 96866, USA.

Over the past three decades, selenium has been intensively investigated as an antioxidant trace element. It is widely distributed throughout the body, but is particularly well maintained in the brain, even upon prolonged dietary selenium deficiency. Changes in selenium concentration in blood and brain have been reported in Alzheimer's disease and brain tumors. The functions of selenium are believed to be carried out by selenoproteins, in which selenium is specifically incorporated as the amino acid, selenocysteine. Several selenoproteins are expressed in brain, but many questions remain about their roles in neuronal function. Glutathione peroxidase has been localized in glial cells, and its expression is increased surrounding the damaged area in Parkinson's disease and occlusive cerebrovascular disease, consistent with its protective role against oxidative damage. Selenoprotein P has been reported to possess antioxidant activities and the ability to promote neuronal cell survival. Recent studies in cell culture and gene knockout models support a function for selenoprotein P in delivery of selenium to the brain. mRNAs for other selenoproteins, including selenoprotein W, thioredoxin reductases, 15-kDa selenoprotein and type 2 iodothyronine deiodinase, are also detected in the brain. Future research directions will surely unravel the important functions of this class of proteins in the brain.

Publication Types:
* Review
* Review, Tutorial

PMID: 12807419 [PubMed - indexed for MEDLINE]

2. Schweizer U, Brauer AU, Kohrle J, Nitsch R, Savaskan NE. Selenium and brain function: a poorly recognized liaison. Brain Res Brain Res Rev. 2004 Jul;45(3):164-78.

Neurobiology of Selenium, Neuroscience Research Center, Charite, University Medical School, Berlin, Germany.

Molecular biology has recently contributed significantly to the recognition of selenium (Se)2 and Se-dependent enzymes as modulators of brain function. Increased oxidative stress has been proposed as a pathomechanism in neurodegenerative diseases including, among others, Parkinson's disease, stroke, and epilepsy. Glutathione peroxidases (GPx), thioredoxin reductases, and one methionine-sulfoxide-reductase are selenium-dependent enzymes involved in

antioxidant defense and intracellular redox regulation and modulation. Selenium depletion in animals is associated with decreased activities of Se-dependent enzymes and leads to enhanced cell loss in models of neurodegenerative disease. Genetic inactivation of cellular GPx increases the sensitivity towards neurotoxins and brain ischemia. Conversely, increased GPx activity as a result of increased Se supply or overexpression ameliorates the outcome in the same models of disease. Genetic inactivation of selenoprotein P leads to a marked reduction of brain Se content, which has not been achieved by dietary Se depletion, and to a movement disorder and spontaneous seizures. Here we review the role of Se for the brain under physiological as well as pathophysiological conditions and highlight recent findings which open new vistas on an old essential trace element.

PMID: 15210302 [PubMed - in process]

3. Burk RF, Hill KE, Motley AK. Selenoprotein metabolism and function: evidence for more than one function for selenoprotein P. J Nutr. 2003 May;133(5 Suppl 1):1517S-20S.

Division of Gastroenterology, Department of Medicine and Clinical Nutrition Research Unit, Vanderbilt University School of Medicine, Nashville, TN 37232-2279, USA. raymond.burk@vanderbilt.edu

Biological functions of selenium are exerted by selenoproteins that contain selenocysteine in their primary structure. Selenocysteine is synthesized and inserted into proteins cotranslationally by a complex process. Families of selenoproteins include the glutathione peroxidases, the iodothyronine deiodinases and the thioredoxin reductases. These are redox enzymes that take advantage of the chemical properties of selenium to catalyze, respectively, removal of hydroperoxides by glutathione, deiodination of thyroid hormones and support of cellular processes requiring reduction of disulfides. Approximately 10 additional selenoproteins have been identified. One of them, selenoprotein P, is an extracellular protein that contains most of the selenium in plasma. It associates with endothelial cells, probably through its heparin-binding properties. Selenoprotein P has been postulated to protect against oxidative injury and to transport selenium from the liver to peripheral tissues. Selenium-dependent protection against diquat-induced liver necrosis and lipid peroxidation in the rat correlates with the presence of selenoprotein P. Recent results support a transport function. When (75)SeO(3)(2-) was administered intravenously to rats, liver tissue took up (75)Se within minutes, associated with a rapid decline in plasma (75)Se. Brain tissue did not begin accumulating (75)Se until (75)Se-labeled selenoprotein P had begun appearing in the plasma after 30 min. These results suggest that tissues like liver can take up small-molecule forms of selenium whereas presence of the element in selenoprotein P facilitates uptake by tissues like brain. Thus, there is evidence for both antioxidant and selenium transport functions of selenoprotein P.

Publication Types:
* Review
* Review, Tutorial

PMID: 12730456 [PubMed - indexed for MEDLINE]

4. Kantola M, Purkunen R, Kroger P, Tooming A, Juravskaja J, Pasanen M, Seppanen K, Saarikoski S, Vartiainen T. Selenium in pregnancy: is selenium an

active defensive ion against environmental chemical stress? Environ Res. 2004 Sep;96(1):51-61.

Department of Chemistry, University of Kuopio, Kuopio, Finland. marjatta.kantola@metla.fi

Transportation of selenium from mother to fetus and its possible effects on mother's zinc, copper, cadmium, and mercury levels were studied together during the first trimester and at term in 216 mothers. Mothers came from three geographical places with different selenium intakes. The role of selenium as a biomarker for the vital function was estimated by studying the associations between tissue or blood selenium content and placental cytochrome P450 enzyme activities and the newborn's birth weight. Regardless of the selenium intake of the mothers, higher concentrations were found in the cord blood than in mother's blood reflecting active transportation of selenium to the fetus. Active smoking was associated with higher placental selenium concentrations like it is associated with higher placental zinc concentrations. When the cadmium concentrations were high in placenta, as in smokers, the transfer of selenium from blood to placenta was increased, decreasing the selenium levels in blood. On the other hand, the high selenium concentrations in blood were connected to lower cadmium concentrations in placenta also in nonsmokers. Selenium had correlations with copper and zinc. ECOD activity in placental tissue, mercury in mothers' hair, mothers' age, and selenium concentrations in cord blood and placental selenium all seem to have connections with xenobiotic-metabolizing enzymes linked effects among mothers. These data suggest that selenium has an active role in the mother's defense systems against the toxicity of environmental pollutants and the constituents of cigarette smoke.

PMID: 15261784 [PubMed - indexed for MEDLINE]

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Department of Mathematics, San Francisco State University, San Francisco, CA 94132, USA.

Selenium has been reported to reduce the risk for heart diseases and cancer. We examined the association of sex, age, geographical location, serum cotinine concentrations, a measure of smoking intensity, and alcohol consumption with serum selenium concentrations in the third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. Study sample consisted of 14,619 apparently healthy individuals (male: 7,102; female: 7,517) aged 14 to >90 years. Sex, age, geographical location, serum cotinine concentrations, and alcohol consumption significantly influenced serum selenium concentrations ($P < 0.05$). The mean (+/- standard error) serum selenium concentration in men (124.5 +/- 0.20 ng/mL) was significantly higher than in women (122.0 +/- 0.20 ng/mL) ($P < 0.0001$). Men in the 31-50 y age group had the highest mean serum selenium concentration. In the same age group, women had the lowest mean serum selenium concentration. In both sexes, participants living in the Midwest and West had significantly higher serum selenium concentrations than those living in South and Northeast geographical locations. Serum cotinine was negatively associated with serum selenium concentrations in both men (beta = -0.0108; $P < 0.0001$ for trend) and women (beta = -0.0097; $P < 0.0001$ for trend). Alcohol consumption is

positively associated with serum selenium in women (beta = 0.0462; P = 0.0044 for trend) but not in men (beta = 0.0015; P = 0.8496 for trend). Although, sex, age, geographical location, smoking, and alcohol intake influenced serum selenium concentrations, clinically low serum selenium concentrations are not common in the USA.

PMID: 12755496 [PubMed - indexed for MEDLINE]

COPPER

Research has demonstrated a link between proper copper utilization and other minerals[1,2,3,4] such as molybdenum, selenium, zinc, and iron. There is also an association between copper deficiency or imbalance and enkephalin deficiency[5], decreased superoxide dismutase[6], and motor function[7].

The following description of copper is taken from *The Merck Manual Second Home Edition.*

Most of the copper in the body is located in the liver, bones, and muscle, but traces of copper occur in all tissues of the body. The liver excretes excess copper into the bile for elimination from the body. Copper is a component of many enzymes. Some of these enzymes are necessary for energy production or for the formation of the hormone epinephrine, red blood cells, bone, or connective tissue (which binds other tissues and organs together). Other enzymes act as antioxidants. They help protect cells against damage by free radicals, which are reactive by-products of normal cell activity.

COPPER DEFICIENCY

Copper deficiency is rare among healthy people. It occurs most commonly among infants who are premature, who are recovering from severe undernutrition, or who have persistent diarrhea. A severe disorder that impairs absorption of nutrients (such as celiac disease, Crohn's disease, cystic fibrosis, or tropical sprue) may cause this deficiency. A high intake of zinc or iron can decrease the absorption of copper.

Symptoms of copper deficiency include fatigue, bleeding under the skin, damage to blood vessels, and an enlarged heart. Anemia is common, and the number of white blood cells is decreased.

The diagnosis of copper deficiency is based on symptoms and on blood tests that detect low levels of copper and ceruloplasmin (a protein that contains copper). Copper deficiency is treated with a copper supplement.

COPPER DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "Copper is a component of … enzymes necessary for energy production or for the formation of the hormone epinephrine, red blood cells, bone, or connective tissue (which binds other tissues and organs together). Other enzymes act as antioxidants. "Symptoms of copper deficiency include fatigue, bleeding under the skin, damage to blood vessels, and an enlarged heart." They can also include osteoporosis because of the connective tissue component of copper's function.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of copper from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems. In the case of copper, common antacids can interfere with its absorption.

COPPER EXCESS

Excess consumption of copper is rare. Any copper not bound to a protein is toxic. Acidic food or beverages in prolonged contact with copper vessels, tubing, or valves can be contaminated with small amounts of unbound copper. Consuming even relatively small amounts of unbound copper may cause nausea, vomiting, and diarrhea. Large amounts can damage the kidneys, inhibit urine production, and cause anemia due to the rupture of red blood cells (hemolysis) and even death.

The diagnosis is made by measuring copper and ceruloplasmin levels in the blood or urine. Treatment involves use of drugs that bind with copper.

COPPER REFERENCES

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Comment in:
* Nature. 2004 Aug 12;430(7001):736-7.

Department of Plant Biology, Technical University, Spielmannstrasse 7, D-38106 Braunschweig, Germany.

The molybdenum cofactor is part of the active site of all molybdenum-dependent enzymes, except nitrogenase. The molybdenum cofactor consists of molybdopterin, a phosphorylated pyranopterin, with an ene-dithiolate coordinating molybdenum. The same pyranopterin-based cofactor is involved in metal coordination of the homologous tungsten-containing enzymes found in archea. The molybdenum cofactor is synthesized by a highly conserved biosynthetic pathway. In plants, the multidomain protein Cnx1 catalyses the insertion of molybdenum into molybdopterin. The Cnx1 G domain (Cnx1G), whose crystal structure has been determined in its apo form, binds molybdopterin with high affinity and participates in the catalysis of molybdenum insertion. Here we present two high-resolution crystal structures of Cnx1G in complex with molybdopterin and with adenylated molybdopterin (molybdopterin-AMP), a mechanistically important intermediate. Molybdopterin-AMP is the reaction product of Cnx1G and is subsequently processed in a magnesium-dependent reaction by the amino-terminal E domain of Cnx1 to yield active molybdenum cofactor. The unexpected identification of copper bound to the molybdopterin dithiolate sulphurs in both structures, coupled with the observed copper inhibition of Cnx1G activity, provides a molecular link between molybdenum and copper metabolism.

PMID: 15306815 [PubMed - indexed for MEDLINE]

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Obstetrics and Gynecology Department, Faculty of Medicine, University of Kuwait, PO Box 24923, 13110, Safat, Kuwait.

OBJECTIVE. The objective was to assess the status of essential trace elements such as copper, iron, molybdenum, selenium and zinc in insulin-dependent diabetic pregnancies at term and to compare the data with a control group. Fetal-maternal

ratios of the elements and copper:zinc ratio were also computed in the control and study populations. METHODOLOGY. Samples from maternal vein, umbilical artery and umbilical vein of diabetic and control women were collected at the time of spontaneous delivery or cesarean section and activities of trace elements evaluated by atomic absorption spectrophotometry. RESULTS. Cu, Fe, Mo, Se and Zn concentrations in maternal venous blood averaged 2,156, 2,020, 13, 102 and 656 microg/l in control women (n=17) while in the diabetic group (n=14), the corresponding values for the trace elements averaged 3,135, 3,675, 15, 85 and 628 microg/l respectively. Values for copper and molybdenum were significantly higher (p<0.05) in the study group compared to control while those of zinc, iron and selenium were not significantly different (p>0.05). Iron and molybdenum values were significantly higher (p<0.05) and that of zinc significantly lower (p<0.05) in umbilical arterial samples of diabetic group compared to controls. In the case of molybdenum, copper the values were significantly higher (p<0.05) in umbilical venous samples of diabetic group compared to that of control. Significant differences in Cu:Zn ratio of maternal venous and umbilical samples and fetal-maternal ratios of some elements were noted between control and study group as well. CONCLUSION. We speculate that altered status of some essential trace elements and altered antioxidant mineral ratio observed in insulin dependent diabetic patients could have deleterious influences on the health of the mother as well as the fetus and newborn.

PMID: 15175885 [PubMed - as supplied by publisher]

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4. Kantola M, Purkunen R, Kroger P, Tooming A, Juravskaja J, Pasanen M, Seppanen K, Saarikoski S, Vartiainen T. Selenium in pregnancy: is selenium an active defensive ion against environmental chemical stress? Environ Res. 2004 Sep;96(1):51-61.

Department of Chemistry, University of Kuopio, Kuopio, Finland. marjatta.kantola@metla.fi

Transportation of selenium from mother to fetus and its possible effects on mother's zinc, copper, cadmium, and mercury levels were studied together during the first trimester and at term in 216 mothers. Mothers came from three geographical places with different selenium intakes. The role of selenium as a biomarker for the vital function was estimated by studying the associations between tissue or blood selenium content and placental cytochrome P450 enzyme activities and the newborn's birth weight. Regardless of the selenium intake of the mothers, higher concentrations were found in the cord blood than in mother's blood reflecting active transportation of selenium to the fetus. Active smoking was associated with higher placental selenium concentrations like it is associated with higher placental zinc concentrations. When the cadmium concentrations were high in placenta, as in smokers, the transfer of selenium from blood to placenta was increased, decreasing the selenium levels in blood. On the other hand, the high selenium concentrations in blood were connected to lower cadmium concentrations in placenta also in nonsmokers. Selenium had correlations with copper and zinc. ECOD activity in placental tissue, mercury in mothers' hair, mothers' age, and selenium

concentrations in cord blood and placental selenium all seem to have connections with xenobiotic-metabolizing enzymes linked effects among mothers. These data suggest that selenium has an active role in the mother's defense systems against the toxicity of environmental pollutants and the constituents of cigarette smoke.

PMID: 15261784 [PubMed - indexed for MEDLINE]

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Twenty-four male subjects participated in a study in which the effect of feeding diets low in copper (1.03 mg/day) on plasma opiates was determined. The subjects were fed a low-copper diet for 11 wk with either starch or fructose as a major source of carbohydrate. Feeding low-copper diet decreased serum copper level significantly. In addition, plasma leu- and met-enkephalins decreased significantly while beta-endorphin levels rose. On repletion with copper (3 mg/day) for 3 wk, plasma enkephalins increased while beta-endorphin levels decreased to pretest values. These results suggest that feeding low copper decreases plasma enkephalins, which may reflect a copper-dependent process affecting enkephalin biosynthesis and/or release.

PMID: 2934971 [PubMed - indexed for MEDLINE]

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United States Department of Agriculture, Agricultural Research Center, Grand Forks Human Nutrition Research Center, ND, USA.

To study the effects of low copper intake in older individuals, 12 postmenopausal women, aged 63.1 +/- 8.8 y, were fed a diet containing 9 micromol (0.57 mg) Cu/d for 105 d, followed by a copper-repletion period of 35 d during which the diet was supplemented with 31.5 micromol (2.0 mg) Cu/d. Plasma copper and ceruloplasmin did not change significantly during copper depletion but ceruloplasmin decreased during copper repletion. Erythrocyte superoxide dismutase activity dropped significantly during low copper intake from 3450 to 2600 U/g hemoglobin, but did not increase during copper repletion. Platelet cytochrome c oxidase activity changed significantly ($P<0.0001$) from 1740 to 810 U/g protein during copper depletion, then increased to 1000 U/g protein during copper repletion. Erythrocyte glutathione peroxidase activity responded similarly. Clotting factor VIII activity increased significantly during copper depletion, then dropped during copper repletion. Low copper intakes did not induce the changes in serum cholesterol and hematology generally found in copper-deficient animal models. These results indicate that a paradigm shift may be needed in evaluating copper status in adult humans. Sensitive indicators of copper include functional activities of platelet cytochrome c oxidase, platelet copper, glutathione peroxidase, and clotting factor VIII. Plasma copper, ceruloplasmin, and cholesterol are relatively insensitive indicators. Also, the recovery from mild copper depletion may require more aggressive intervention tha 2 mg Cu/d for 35 d.

PMID: 8602593 [PubMed - indexed for MEDLINE]

7. Penland JG, Prohaska JR. Abnormal motor function persists following recovery from perinatal copper deficiency in rats. J Nutr. 2004 Aug;134(8):1984-8.

U.S. Department of Agriculture ARS Human Nutrition Research Center, Grand Forks ND, 58202, USA.

What are the biochemical and behavioral consequences of perinatal copper deficiency? Pregnant Holtzman rats were fed a modified AIN-76A diet low in copper (0.34 mg Cu/kg and 42 mg Fe/kg) starting on gestation d 7. Seven rats received copper in their drinking water (20 mg Cu/L) (+Cu) and 7 drank deionized water (-Cu). Treatments did not affect litter size or pregnancy outcome. Compared with +Cu dams and a sample of +Cu male weanling [postnatal day (P)21] offspring, -Cu rats exhibited signs consistent with copper deficiency. P21 males were switched to a nonpurified copper-adequate diet and sampled biochemically after 3 mo and behaviorally after 3 and 6 mo of repletion (CuR). Compared with controls, CuR rats had lower brain copper and iron levels 3 and 6 mo after repletion; other biochemical differences were not detected. Behavioral assessments after 5 mo of repletion indicated a persistent impairment in motor function of CuR compared with control rats as evaluated by the accelerating rotorod procedure. These results suggest that permanent impairment to motor function can persist after long-term recovery from perinatal copper deficiency.

PMID: 15284387 [PubMed - indexed for MEDLINE]

MANGANESE

Manganese deficiency or imbalance has been linked to symptoms of aggression[1,2,3,4], ADHD[5,6,7], and schizophrenia[8,9,10,11,12].

The following description of manganese is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

Manganese (Mn) is a component of several enzyme systems, including manganese-specific glycosyltransferases and phosphoenolpyruvate carboxykinase, and is essential for normal bone structure. Intake varies greatly, depending mainly on the consumption of rich sources, such as unrefined cereals, green leafy vegetables, and tea. The usual intake of this mineral is 2 to 5 mg/day, and absorption is 5 to 10%.

One case of human manganese deficiency was reported in a volunteer who received a purified diet containing 0.1 mg/day of manganese. He developed transient dermatitis, hypocholesterolemia, and an increase in alkaline phosphatase levels. He lost about 60% of his estimated body pool of manganese in 2 wk, but no further losses occurred during an additional 4 wk on a deficient diet. Manganese deficiency has not been documented in the clinical literature.

Manganese poisoning is usually limited to people who mine and refine ore; prolonged exposure causes neurologic symptoms resembling parkinsonism or Wilson's disease.

MANGANESE DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation "Manganese is a component of several enzyme system and is essential for normal bone structure. We are dependent on eating foods that are rich in manganese, such as "unrefined cereals and green leafy vegetables".

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack manganese from lack of essential nutrients found in vegetables, and whole grains, which leads to a host of health problems.

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CHROMIUM

Observational and experimental studies have shown an association between chromium deficiency or imbalance and depression[1,2,3,4].

The following description of chromium is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

The evidence for chromium (Cr) as an essential trace mineral in animals was obtained in rats fed a Torula yeast-based diet. They developed abnormal glucose tolerance that could be reversed by supplements of brewer's yeast, thought to contain a glucose tolerance factor. Trivalent chromium (CrCl3) was later reported to be the active factor in brewer's yeast. Further, it was reported that chromium formed a complex with insulin that enhanced insulin's activity. However, the relevance of animal studies of chromium deficiency to the effects of chromium in humans remains controversial. Glucose tolerance factor has never been isolated nor its structure determined. The insulin receptor has been purified and characterized without finding any evidence of chromium as a component of its subunits, as an accessory chromoprotein for insulin binding, or as a second messenger in mediating the effect of insulin on cells. Unlike iron, zinc, copper, molybdenum, and selenium, chromium has not been found in a metalloprotein with biologic activity. Therefore, the apparent biologic activity of chromium in promoting glucose tolerance remains unexplained.

The estimated requirement for chromium in humans is about 1 μg/day, but only 1 to 3% of trivalent chromium is absorbed. In the USA, chromium intakes range from 20 to 50 μg/day, with plasma levels from 0.05 to 0.50 μg/L (1.0 to 9.6 nmol/L). The Food and Nutrition Board of the NAS/NRC states that a safe, adequate intake of chromium for an adult is 50 to 200 μg/day.

Deficiency: Apparent chromium deficiency that was associated with glucose intolerance and peripheral neuropathy occurred in four patients receiving long-term TPN. Three responded to doses of 150 to 250 μg of trivalent chromium, with a reduction in peripheral neuropathy and an increase in glucose tolerance.

Interestingly the *The Merck Manual Second Home Edition*, for health consumers and not necessarily professionals, is far more open-minded in its description of chromium than the Merck Manual for doctors.

CHROMIUM PICOLINATE

Background: Chromium is a mineral required in small quantities by the body. It enables insulin to function normally and helps the body process (metabolize) carbohydrates and fats. Good sources of chromium include carrots, potatoes, broccoli, whole-grain products, and molasses. Picolinate, a by-product of the amino acid tryptophan, is paired with chromium in supplements because it is claimed to help the body absorb chromium more efficiently.

CHROMIUM DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation chromium "enables insulin to function normally and helps the body process (metabolize) carbohydrates and fats". These remarkable functions are dependent on food sources of chromium from "carrots, potatoes, broccoli, whole-grain products, and molasses".

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of chromium from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

CHROMIUM REFERENCES

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MOLYBDENUM

Research has demonstrated a link between molybdenum deficiency or imbalance and convulsions[1], neurologic problems[2], normal development[3], detoxification[4].

The following description of molybdenum is taken from *The Merck Manual of Diagnosis and Therapy* (Seventeenth Edition).

Molybdenum (Mo) is a transition metal that forms oxides and is a component of a pterin coenzyme essential for the activity of xanthine oxidase, sulfite oxidase, and aldehyde oxidase. Genetically conditioned sulfite oxidase deficiency was described in 1967 in a child with mental retardation, convulsions, opisthotonus, and lens dislocation. This disorder was due to the child's inability to form the molybdenum coenzyme despite the presence of adequate molybdenum.

Sulfite toxicity due to molybdenum deficiency was noted in a patient on long-term TPN who developed tachycardia, tachypnea, headache, nausea, vomiting, and coma. A metabolic study showed high levels of sulfite and xanthine and low levels of sulfate and uric acid in his blood and urine, which led to the diagnosis. Giving ammonium molybdate 300 μg/day IV led to a dramatic recovery. Both genetically conditioned and nutritional deficiencies of molybdenum are rare. The intake of molybdenum varies from 100 to 500 μg/day and is derived principally from organ meats, whole-grain cereals, and legumes.

The Food and Nutrition Board of the NAS/NRC (National Academy of Sciences and National Research Council) states that a safe, adequate intake of molybdenum is 75 to 250 μg/day for adults and 25 to 75 μg/day for children aged 1 to 6 yr.

MOLYBDENUM DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation molybdenum is a necessary component of several oxidase enzymes. One enzyme is responsible for detoxification of sulfite, a preservative and also a normal food constituent.

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of molybdenum from lack of essential nutrients found in fresh fruits, vegetables, and whole grains, which leads to a host of health problems.

MOLYBDENUM REFERENCES

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Academic Medical Center, Department of Neonatology, Amsterdam, The Netherlands.

Intractable seizures in the neonatal period may be caused by molybdenum-cofactor deficiency, an inborn error which combines the deficiencies of sulphite oxidase and

xanthine dehydrogenase. The neurological symptoms of molybdenum cofactor and isolated sulphite oxidase deficiencies are identical. Two new cases are reported, and the literature on neonatal convulsions due to molybdenum-cofactor and sulphite deficiencies is reviewed. Because of the high incidence of neonatal convulsions a search for this deficiency is advocated in each case of unexplained refractory neonatal convulsions. Diagnosis may be missed or delayed on standard metabolic screening for several reasons discussed. By simply using a sulphite strip test in a fresh urine sample an indication for the defect can be obtained. Antenatal diagnosis can be performed by assay of sulphite oxidase activity in a chorionic villus sample.

Publication Types:
* Case Reports

PMID: 8355818 [PubMed - indexed for MEDLINE]

2. Sardesai VM. Molybdenum: an essential trace element. Nutr Clin Pract. 1993 Dec;8(6):277-81.

Molybdenum is found in most foods, with legumes, dairy products, and meats being the richest sources. This metal is considered essential because it is part of a complex called molybdenum cofactor that is required for the three mammalian enzymes xanthine oxidase (XO), aldehyde oxidase (AO), and sulfite oxidase (SO). XO participates in the metabolism of purines, AO catalyzes the conversion of aldehydes to acids, and SO is involved in the metabolism of sulfur-containing amino acids. Molybdenum deficiency is not found in free-living humans, but deficiency is reported in a patient receiving prolonged total parenteral nutrition with clinical signs characterized by tachycardia, headache, mental disturbances, and coma. The biochemical abnormalities in this acquired molybdenum deficiency include very low levels of uric acid in serum and urine (low XO activity) and low inorganic sulfate levels in urine (low SO activity). Inborn errors of isolated deficiencies of XO, SO, and molybdenum cofactor are described. Although XO deficiency is relatively benign, patients with isolated deficiencies of SO or molybdenum cofactor exhibit mental retardation, neurologic problems, and ocular lens dislocation. These abnormalities seem to be caused by the toxicity of sulfite and/or inadequate amounts of inorganic sulfate available for the formation of sulfated compounds present in the brain. XO and AO may also participate in the inactivation of some toxic substances, inasmuch as studies suggest that molybdenum deficiency is a factor in the higher incidence of esophageal cancer in populations consuming food grown in molybdenum-poor soil.

PMID: 8302261 [PubMed - indexed for MEDLINE]

3. Mancinella A. Molybdenum: an indispensible trace element in normal human development. Clin Ter. 1993 May;142(5):459-64.

[Article in Italian]

I Divisione di Geriatria, USL, Ospedale Addolorata Roma.

Having briefly analyzed the role of molybdenum in the metabolism of living organisms, the author describes conditions induced by molybdenum deficit and poisoning due to this metal. The most recent acquisitions concerning the importance of this element for normal development of the human organism are also illustrated.

Publication Types:
* Review
* Review, Tutorial

PMID: 8339529 [PubMed - indexed for MEDLINE]

4. Neve J. The nutritional importance and physiopathology of molybdenum in man. J Pharm Belg. 1991 May-Jun;46(3):189-96.

[Article in French]

Institut de Pharmacie, Universite Libre de Bruxelles.

Molybdenum is an essential trace element taking part in the active site of three human enzymes: xanthine oxidase, aldehyde oxidase and sulfite oxidase, playing a role in the detoxification of the organism and/or the production of important intermediary products. The perturbation of the first two enzymes has no established clinical consequence, but a decrease in activity of the third one is harmful for the organism, particularly the nervous system during pre- or post-natal development. The anomalies in the function of these enzymes are generally inherited and linked to the impaired production of the molybdenum cofactor, an organic molecule complexed to the element in the active site. However, several pathological cases in animals and one case in man have been clearly attributed to molybdenum deficiency. It is the reason why molybdenum supplementation has been recommended in long term total parenteral nutrition in infants and adults.

Publication Types:
* Review
* Review, Tutorial

PMID: 1757880 [PubMed - indexed for MEDLINE]

IRON

Research has demonstrated a link between iron deficiency or imbalance and heme production[1], inflammatory bowel disease[2], spinda bifida[3], brain disorders[4], thyroid function[5], lead toxicity[6,7].

The following description of iron is taken from *The Merck Manual Second Home Edition.*

Much of the iron in the body occurs in hemoglobin. Hemoglobin is the component of red blood cells that enables them to carry oxygen and deliver it to the body's tissues. Iron is an important component of hemoglobin and muscle cells. Iron is also necessary for the formation of many enzymes in the body.

The body recycles iron: When red blood cells die, the iron in them is returned to the bone marrow to be used again in new red blood cells. A small amount of iron is lost each day, mainly in cells shed from the lining of the intestine. This amount is usually replaced by the 1 to 2 milligrams of iron absorbed from food each day.

Food contains two types of iron: heme iron (found in animal products) and nonheme iron (found in most foods and in iron supplements). Nonheme iron accounts for more than 85% of iron in the average diet. However, less than 20% of nonheme iron that is consumed is absorbed into the body. Nonheme iron is absorbed better when it is consumed with animal protein and with vitamin C. Heme iron is absorbed much better than nonheme iron.

IRON DEFICIENCY

Iron deficiency is the most common mineral deficiency in the world, causing anemia in men, women, and children.

In adults, iron deficiency is most commonly caused by loss of blood. In premenopausal women, monthly menstrual bleeding may cause the deficiency. In men and postmenopausal women, iron deficiency usually indicates bleeding in the digestive tract--for example, from a bleeding ulcer or a polyp in the colon. The deficiency may also result from bleeding in other areas of the body, such as the kidneys.

Iron deficiency may result from an inadequate diet, primarily in infants and small children, who need more iron because they are growing. Adolescent girls who do not eat meat are at risk of developing iron deficiency because they are growing and starting to menstruate. Pregnant women are also at risk of this deficiency, because the growing fetus requires large amounts of iron.

Symptoms

When iron reserves in the body are exhausted, anemia develops (see Section 14, Chapter 172). Anemia causes paleness, weakness, irritability, drowsiness, and fatigue. Concentration and learning ability may be impaired. When severe, anemia may cause headache, ringing in the ears (tinnitus), spots before the eyes, digestive upset, shortness of breath, dizziness, and a rapid heart rate. Occasionally, severe anemia causes chest pain and heart failure. Menstrual periods may stop.

In addition to anemia, iron deficiency may produce such symptoms as pica (a craving for nonfoods such as ice, dirt, or pure starch), spoon nails (a deformity in

which the fingernails are thin and concave), and leg cramps at night. Rarely, iron deficiency may cause a thin membrane to grow across part of the esophagus, resulting in difficulty swallowing.

Diagnosis

The diagnosis of iron deficiency is based on symptoms and on blood test results. Results include a low level of hemoglobin (which contains iron), a low hematocrit (the proportion of red blood cells to the total volume of blood), and a low number of red blood cells, which are abnormally small. The amount of iron in transferrin--the protein that carries iron in blood when iron is not inside red blood cells--is determined. If the amount is less than 10%, iron deficiency is likely. Iron deficiency is confirmed if the level of ferritin (a protein that stores iron) in the blood is low. However, inflammation, infection, cancer, or liver damage can result in a normal or high ferritin level even when iron deficiency is present.

Treatment

Because the most common cause of iron deficiency in adults is excessive bleeding, doctors first look for a source of bleeding. Drugs, such as oral contraceptives (birth control pills), may be needed to control excessive menstrual bleeding. Surgery may be needed to repair a bleeding ulcer or remove a polyp in the colon. A blood transfusion may be necessary if the anemia is severe.

General treatment includes daily doses of an iron supplement taken by mouth. Normal dietary intake of iron may not be sufficient to replace lost iron (because less than 20% of iron in a typical diet is absorbed into the body). Iron is absorbed best when the supplement is taken on an empty stomach, 30 minutes before meals or 2 hours after meals, particularly if the meals include foods that reduce the absorption of iron (such as vegetable fibers, phytates, bran, coffee, and tea). However, taking iron supplements on an empty stomach can cause indigestion and constipation. So some people must take the supplements with meals. Antacids and calcium supplements can also reduce iron absorption. Consuming vitamin C in juices or taking it as a supplement enhances iron absorption. Eating small amounts of meat, which contains the easily absorbed form of iron (heme iron), enhances the absorption of the poorly absorbed form of iron (nonheme iron). Iron supplements almost always turn stools black--a harmless side effect.

Rarely, iron is given by injection. Injections are necessary for people who cannot tolerate tablets or for a few people who cannot absorb enough iron from the digestive tract.

Correcting iron deficiency anemia usually takes 3 to 6 weeks, even after the bleeding has stopped. After the anemia is corrected, an iron supplement should be taken for 6 months to replenish the body's reserves. Blood tests are usually performed periodically to determine whether the person is receiving enough iron and to check for continued bleeding.

Women who are not menstruating and men should not take iron supplements or multiple vitamins with iron unless specifically instructed to do so by a doctor. Taking such supplements can make diagnosing bleeding from the intestine difficult. Such bleeding may be due to serious disorders including colon cancer.

Because a developing fetus requires iron, iron supplements are recommended for most pregnant women. Most babies, particularly those who are premature or who

have a low birth weight, need an iron supplement. It is given as an iron-fortified formula or, to breastfed babies, as a separate liquid supplement.

IRON DEFICIENCY AND THE NORTH AMERICAN POPULATION

As noted in the Merck Manual citation iron "Iron deficiency is the most common mineral deficiency in the world, causing anemia in men, women, and children."

In the "Nutrition and Deficiency of Micronutrients" reference section we cite Cleghorn, 2004, who states that "Good nutrition continues to be the cornerstone for survival, health and appropriate development for current and succeeding generations. Well-nourished children perform better in school, grow into healthy adults and in turn give their children a better start in life." We also maintain that children and adults develop malnutrition, including a lack of iron from lack of essential nutrients found in fresh whole foods, which leads to a host of health problems.

IRON EXCESS

Excess iron can accumulate in the body. Causes include many blood transfusions and iron therapy given in excessive amounts or for too long. Another cause is hemochromatosis, a hereditary disorder. Excess iron consumed all at once causes vomiting, diarrhea, and damage to the intestine. Excess iron consumed over a period of time may damage coronary arteries. Treatment often consists of the drug deferoxamine, which binds with iron and carries it out of the body in urine. Treatment of hemachromatosis consists of bloodletting (phlebotomy).

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Heme, the major functional form of iron, is synthesized in the mitochondria. Although disturbed heme metabolism causes mitochondrial decay, oxidative stress, and iron accumulation, all of which are hallmarks of ageing, heme has been little studied in nutritional deficiency, in ageing, or age-related disorders such as Alzheimer's disease (AD). Biosynthesis of heme requires Vitamin B(6), riboflavin, biotin, pantothenic acid, and lipoic acid and the minerals zinc, iron, and copper, micronutrients are essential for the production of succinyl-CoA, the precursor for porphyrins, by the TCA (Krebs) cycle. Only a small fraction of the porphyrins synthesized from succinyl-CoA are converted to heme, the rest are excreted out of the body together with the degradation products of heme (e.g. bilirubin). Therefore, the heme biosynthetic pathway causes a net loss of succinyl-CoA from the TCA cycle. The mitochondrial pool of succinyl-CoA may limit heme biosynthesis in deficiencies for micronutrients (e.g. iron or biotin deficiency). Ageing and AD are also associated with hypometabolism, increase in heme oxygenase-1, loss of complex IV, and iron accumulation. Heme is a common denominator for all these changes, suggesting that heme metabolism maybe altered in age-related disorders. Heme can also be a prooxidant: it converts less reactive oxidants to highly reactive free radicals. Free heme has high affinity for different cell structures (protein, membranes, and DNA), triggering site-directed oxidative damage. This review

discusses heme metabolism as related to metabolic changes seen in ageing and age-related disorders and highlights the possible role in iron deficiency.

PMID: 15231238 [PubMed - in process]

2. Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. Gut. 2004 Aug;53(8):1190-7.

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Iron deficiency anaemia is one of the most common disorders in the world. Also, one third of inflammatory bowel disease (IBD) patients suffer from recurrent anaemia. Anaemia has significant impact on the quality of life of affected patients. Chronic fatigue, a frequent IBD symptom itself, is commonly caused by anaemia and may debilitate patients as much as abdominal pain or diarrhoea. Common therapeutic targets are the mechanisms behind anaemia of chronic disease and iron deficiency. It is our experience that virtually all patients with IBD associated anaemia can be successfully treated with a combination of iron sucrose and erythropoietin, which then may positively affect the misled immune response in IBD.

Publication Types:
* Review
* Review Literature

PMID: 15247190 [PubMed - indexed for MEDLINE]

3. Groenen PM, van Rooij IA, Peer PG, Ocke MC, Zielhuis GA, Steegers-Theunissen RP. Low maternal dietary intakes of iron, magnesium, and niacin are associated with spina bifida in the offspring. J Nutr. 2004 Jun;134(6):1516-22.

Department of Epidemiology and Biostatistics, University Medical Center, Nijmegen, The Netherlands.

Evidence about the preventive effects of nutrients other than folate on the occurrence of spina bifida is scarce. Therefore, the aim of this work was to investigate the role of maternal nutritional intake and the risk of spina bifida in the offspring. In 106 cases and 181 controls, the mothers' nutrient intakes were obtained by an FFQ approximately 24 mo after conception of the index pregnancy. Energy-adjusted mean nutrient intakes were compared, and odds ratios (OR) and 95% CI were calculated. Although mean nutrient intakes were comparable to the Dutch food consumption survey data, fat, cholesterol, iron, and folate intakes were below the 1998 Dutch Recommended Daily Allowances. Case mothers had significantly lower intakes of plant proteins (7%), polysaccharides (4%), fiber (7%), iron (6%), magnesium (6%), and niacin (4%) than control mothers. Mono- and disaccharide intakes were significantly higher (6%) in the case mothers than in control mothers. The adjusted OR (95% CI) in the lowest quartiles for plant proteins was 5.4 (2.3-12.4), for fiber 3.1 (1.5-6.8), for iron 3.5 (1.4-8.3), for magnesium 1.9 (0.9-4.1), and for niacin 2.5 (1.2-5.2). Mono- and disaccharide and polysaccharide intakes in the highest quartile had ORs (95% CI) of 2.9 (1.4-6.3) and 0.5 (0.3-1.0), respectively. The nutritional intake of Dutch women from food groups containing iron and folate seems to be compromised. Low preconceptional intakes

of plant proteins, iron, magnesium, and niacin are associated with a 2- to 5-fold increased risk of spina bifida.

PMID: 15173422 [PubMed - indexed for MEDLINE]

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Department of Laboratory Medicine, University of Washington, Seattle 98104, USA.

Iron is the most important element in the body, essential for almost all types of cells, including brain cells. The role of iron in the brain has been known for years. Iron deficiency and iron excess have been associated with pathophysiology of different brain disorders. Iron deficiency has been reported to have a role in brain development and the pathophysiology of restless legs syndrome. Iron accumulation has been related to some neurologic disorders such as Alzheimer disease, Parkinson disease, type I neurodegeneration with brain iron accumulation, and other disorders. Despite years of investigation, the reason for iron imbalance in the brain is not known. It also is not known whether the accumulation of iron in the brain is primary or secondary to development of neurodegenerative disorders. This review summarizes the present knowledge on the role of iron in human brain disorders.

Publication Types:
* Review
* Review, Tutorial

PMID: 15298151 [PubMed - indexed for MEDLINE]

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PMID: 15255447 [PubMed - indexed for MEDLINE]

6. Wolf AW, Jimenez E, Lozoff B. Effects of iron therapy on infant blood lead levels. Pediatr. 2003 Dec;143(6):789-95.

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OBJECTIVES: To determine the effects of iron therapy on blood lead levels in infants with mildly elevated lead levels and varied iron status. METHODS: Infants from a community-derived sample in Costa Rica were categorized into five groups. Group 1 had iron-deficiency anemia with hemoglobin levels <or=105 g/L. Infants in group 2 were iron-deficient with intermediate hemoglobin levels (between 106-119 g/L). These groups were treated with intramuscular iron or 3 months of oral iron. Group 3 (nonanemic iron-deficient) and group 4 (nonanemic iron-depleted) were treated with 3 months of oral iron. Group 5 (iron-sufficient) received oral placebo. RESULTS: After 3 months of oral iron therapy, nonanemic iron-depleted infants had the greatest decrease in lead levels, followed by nonanemic iron-deficient infants and iron-deficient infants with hemoglobin levels <120 g/L. Lead levels increased among iron-deficient infants with hemoglobin levels <120 g/L who received intramuscular iron and iron-sufficient nonanemic infants who received placebo. CONCLUSIONS: Changes in lead levels corresponded closely to changes

in iron status and were plausible in terms of absorption mechanisms for lead and iron. Correcting and/or preventing iron deficiency appear to be rapid and effective means of improving infant lead levels, even in nonanemic infants.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 14657829 [PubMed - indexed for MEDLINE]

7. Rhodes D, Spiro A 3rd, Aro A, Hu H. Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study. J Occup Environ Med. 2003 Nov;45(11):1144-51.

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Blood and bone lead levels were used to investigate lead's potential effect on psychiatric symptoms among middle-aged to elderly men from the Normative Aging Study. Symptoms were assessed using the Brief Symptom Inventory (BSI) and analyzed as individual outcomes as well as a measure that combined anxiety, depression, and phobic anxiety. Blood and bone lead averaged 6.3 microg/dL (standard deviation [SD] = 4.16), 21.9 microg/g (SD = 13.5), and 32.1 microg/g (SD = 19.8) for blood, tibia, and patella lead, respectively. In logistic regression models that adjusted for age, alcohol intake, employment status, and education status, we found that patella bone lead was significantly associated with an increased risk of phobic anxiety and the combined outcome measure at the P </= 0.05 level. Tibia and blood lead had similar associations. We conclude that cumulative lead exposure, which bone lead levels reflect, could be a risk factor for psychiatric symptoms even at modest levels of exposure.

PMID: 14610395 [PubMed - indexed for MEDLINE]

CITRUS BIOFLAVANOIDS

Research has shown citrus bioflavonoids to have a neuro-protective effects[1,2,3,4].

The citrus bioflavonoid complex used in VitaMind™ consists of natural derivatives of lemon, orange, grapefruit, lime and tangerine. The strong antioxidant activity of citrus bioflavonoids is behind their many health benefits: enhancing the effectiveness of vitamin C; helping to maintain healthy blood vessels by helping to reduce total and LDL-cholesterol levels; strengthening capillaries and regulating their permeability, thereby helping to reduce symptoms of atherosclerosis; helping to ease bruising and to prevent inflammation. Citrus bioflavonoids are also excellent natural antimicrobial agents. Furthermore, they may be instrumental in inhibiting cancer-causing compounds and, thus, may have potential chemo-therapeutic value. Studies have shown that several citrus bioflavonoids, including naringin, naringenin, quercetin and kaempferol, interfere with the activity of certain enzymes that otherwise breakdown certain drugs, resulting in higher levels of these drugs occurring in the blood. Some drugs known to be affected include calcium channel blockers, estrogen, sedatives, medications for high blood pressure, allergies, AIDS, and cholesterol-lowering agents. Caffeine levels and effects of caffeine may also be extended. The overall effect on drug metabolism can be to increase effectiveness. However, it can also result in dosages that are inadvertently too high. This has led to numerous reports advising against taking any drugs with grapefruit juice or citrus bioflavonoid supplements, unless the interaction effect with the drug is known. The amount of citrus bioflavonoid complex used in the VitaMind™ formulation is optimized to potentiate the medicinal/therapeutic effects of the other ingredients of the formulation, without incurring adverse effects. Citrus bioflavonoids are generally considered extremely safe and free of adverse side effects, even during pregnancy.

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GRAPE SEED EXTRACT

Grape seed extract has been demonstrated to have neuro-protective effects[1,2,3,4].

The strong antioxidant properties of the tannins in grape seed extract have been well documented. Studies have shown that grape seed extract is a more efficient antioxidant than either vitamin C or E. Clinical studies have shown that grape seed extract helps to reduce the risk of atherosclerosis and increase vascular strength. In Europe, it has been used for the treatment of various vascular (vessel) disorders that benefit from increased blood flow, e.g. diabetes, leg cramps, varicose veins, arm and leg numbness or tingling, and impotence. Studies have also demonstrated the ability of grape seed extract to promote eye health, i.e. by reducing the risk of macular degeneration and cataracts, likely by improving blood flow to the ocular region of the body. Grape seed extract has also been shown to help reduce the risk of developing certain cancers and to reduce edema (inflammation/swelling).

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CHOLINE

Studies have demonstrated a benefit in the use of choline to reduce symptoms of bipolar disorder[1,2,3,4,5].

Choline is essential in the building and maintenance of cell structure. It is also a component of acetylcholine, which plays a key role in the transmission of nerve impulses. Choline is believed to have anti-inflammatory effects in asthma sufferers by lowering lipophosphatidylcholine levels. It has commonly been referred to as the "lipotropic factor" due to its essential role in fat metabolism. Folic acid and vitamin B12 are needed to process choline in the body. As a supplement, choline is believed to help in the treatment of a broad range of disorders: liver diseases, Tourette's disease, the loss of muscle coordination, involuntary muscle spasms, complex partial seizures, asthma, depression, memory loss, schizophrenia, Alzheimer's disease and dementia. It is also important for brain development, increasing energy levels and delaying the onset of fatigue, reducing high cholesterol, and protecting against cardiovascular disease and cancer development.

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INOSITOL

Research has demonstrated a link between inositol deficiency or imbalance and psychiatric disorders[1,2,3,4], panic disorder[5,6], obsessive compulsive disorder[7,8], and depression[9].

Related chemically to glucose, this B vitamin is required for many different functions within the body, including fat transport and utilisation, maintaining healthy skin and hair, calming the nervous system, maintenance of liver function and preventing the accumulation of fat in the liver, other organs and the vascular system. It is also involved in the synthesis of RNA and is an essential structural component of cell membranes. There is clinical evidence to suggest that inositol supplements may have benefits similar to the conventional drugs used to treat panic disorder, depression, and obsessive-compulsive disorder. Inositol has been used as a supplement to help treat nerve damage often associated with diabetes, and for conditions associated with disorders of fat transport and metabolism, high cholesterol, insomnia, polycystic ovary syndrome, cancer, schizophrenia, Alzheimer's disease, attention deficit-hyperactivity disorder (ADHD) and autism. It has also been used to promote hair growth.

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GINKGO BILOBA

Ginkgo biloba has been shown to have neuro-protective properties[1,2,3,4,5] and to help reduce symptoms of anxiety[6], and lowering cortisol release[7].

Like other flavonoids those from Ginkgo have antioxidant and free radical scavenging properties that prevent or reduce cell membrane lipid peroxidation and decrease oxidative damage to red blood cells. Ginkgo's flavonoids also protect neurons and the eyes from oxidative stress and injury, which may prevent progression of tissue degeneration in patients with dementia and other conditions. Ginkgo's anti-inflammatory effects can benefit individuals with central nervous system (CNS) disorders, including dementia, and other conditions including peripheral arterial disease, hypersensitivity disorders, allergies, asthma, and bronchitis. Ginkgo may be helpful for conditions associated with cerebral vascular insufficiency, especially in the elderly, including memory loss, headache, tinnitus, vertigo, dizziness, difficulty concentrating, mood disturbances, and hearing disorders. Cognitive function has been shown to improve in some elderly people with mild to moderate age-related memory impairment. In several studies, ginkgo has modestly improved some measures of cognitive function, particularly short-term visual memory, and increased the rate of cognitive processing in non-demented patients with age-related memory impairment. Ginkgo may improve memory and speed of cognitive processing, including increasing speed of performance on factors requiring concentration and focused attention in people with no complaints of memory impairment. The specific Ginkgo constituents, ginkgolides A and B, have been shown to decrease glucocorticoid biosynthesis, which might play a role in ginkgo's anti-stress and neuroprotective effects. Ginkgo may improve cognitive behavior and sleep patterns in individuals with depression, and may prevent winter depression. Taking ginkgo for vertigo and equilibrium disorders helps to improve associated symptoms. Ginkgo leaf may also be helpful to prevent acute mountain sickness, aging, to regulate gastric acidity, improve liver and gallbladder function, regulate bacterial flora, control blood pressure, and treat Raynaud's disease. Ginkgo may be beneficial for cognitive disorders secondary to depression; eye problems, including macular degeneration and glaucoma; attention deficit-hyperactivity disorder (ADHD); thrombosis; heart disease; arteriosclerosis; angina pectoris; hypercholesterolemia; cardiac reperfusion injury; premenstrual syndrome (PMS); diabetic retinopathy; as a digestive aid to protect against dysentery and filariasis; in the treatment of respiratory ailments; as a tonic for memory loss in the elderly; and as a longevity elixir.

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The standardized extract of Ginkgo biloba (EGb 761) was found not only to improve memory and aging associated cognitive deficits but also to exert beneficial effects on mood. An antistress action of the extract has been suggested but not directly proven. The present study was aimed to evaluate the effects of EGb 761 on salivary cortisol and blood pressure responses during stress in healthy young volunteers (n = 70) in a double blind placebo controlled design. A stress model involving a combination of static exercise (handgrip) and mental stimuli was used. Single treatment with EGb 761 (120 mg) reduced stress-induced rise in blood pressure without affecting the heart rate. Salivary cortisol responses showed differences with respect to the gender and the time of day of the stress exposure, with the activation only in male subjects in the afternoon. This activation was absent if they were treated with EGb 761. The performance in a short memory test with higher scores achieved by women remained unaffected by EGb 761 treatment. Thus, this study provides evidence that EGb 761 has an inhibitory action on blood pressure and it may influence cortisol release in response to some stress stimuli.

Publication Types:
* Clinical Trial
* Randomized Controlled Trial

PMID: 12369732 [PubMed - indexed for MEDLINE]

METHIONINE

A methionine deficiency or imbalance has been shown to be associated with depression[1,2,3], premenstrual syndrome[4,5], and schizophrenia[2,3,6,7], and cognitive disease[8].

The following description of methionine is taken from the 2003, PDR For Non Prescription Drugs and Supplements. (Thompson Healthcare)

L-METHIONINE

L-methionine is a protein amino acid. It is classified as an essential amino acid for humans and therefore must be supplied in the diet. According to the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO), recommended daily L-methionine intake is 13 mg per kg or about one gram daily for adults. Actual intake is higher. This is principally derived from dietary proteins. Rich sources of L-methionine include cheeses, eggs, fish, meat and poultry. L-methionine is also found in fruits and vegetables, but not as abundantly. Small amounts of free L-methionine occur in vegetables, vegetable juices and fermented foods.

In addition to its role as a precursor in protein synthesis, L-methionine participates in a wide range of biochemical reactions, including the production of S-adenosylmethionine (SAM or SAMe), L-cysteine, glutathione, taurine and sulfate. SAM itself, as a methyl donor (see SAMe), is involved in the synthesis of creatine, epinephrine, melatonin and the polyamines spermine and spermidine, among several other substances.

L-methionine is also a glycogenic amino acid and may participate in the formation of D-glucose and glycogen. The ability of L-methionine to reduce the liver-toxic effects of such hepatotoxins as acetaminophen and methotrexate has led to the suggestion that methionine should be added to acetaminophen products. However, there is some recent research suggesting that elevated L-methionine intake may promote intestinal carcinogenesis. This is unclear. Further, one of the metabolites of L-methionine, L-homocysteine, has been implicated as a significant factor in coronary heart disease and other vascular diseases.

L-methionine is a sulfur-containing amino acid that is minimally soluble in water. Its molecular formula is C5H11NO2S, and its molecular weight is 149.21 daltons. L-methionine is also known as 2-amino-4-(methylthio)butyric acid, alpha-amino-gamma-methylmercaptobutyric acid, (S)-2-amino-4-(methylthio)butanoic acid and gamma-methylthio-alpha-aminobutyric acid. It is abbreviated as Met and its one-letter abbreviation is M. The terms L-methionine and methionine are used interchangeably. The D-stereoisomer, D-methionine, does not possess biological activity with regard to protein synthesis and the biochemical reactions mentioned above. However, D-methionine, as well as L-methionine, may possess antioxidant activity. L-methionine is represented by the following chemical structure:

ACTIONS

L-methionine may protect against the toxic effects of hepatotoxins, such as acetaminophen. Methionine may have antioxidant activity.

Mechanism of Action

The mechanism of the possible anti-hepatotoxic activity of L-methionine is not entirely clear. It is thought that metabolism of high doses of acetaminophen in the liver lead to decreased levels of hepatic glutathione and increased oxidative stress. L-methionine is a precursor to L-cysteine. L-cysteine itself may have antioxidant activity. L-cysteine is also a precursor to the antioxidant glutathione. Antioxidant activity of L-methionine and metabolites of L-methionine appear to account for its possible anti-hepatotoxic activity. Recent research suggests that methionine itself has free-radical scavenging activity by virtue of its sulfur, as well as its chelating ability.

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Homocysteine, a sulfur-containing amino acid, is a metabolite of the essential amino acid methionine, and exists at a critical biochemical intersection in the methionine cycle - between S-adenosylmethionine, the indispensable ubiquitous methyl donor, and vitamins B12 and folic acid. High blood levels of homocysteine signal a breakdown in this vital process, resulting in far-reaching biochemical and life consequences. The link between homocysteine and cardiovascular disease is well established, and decreasing plasma total homocysteine by providing nutritional cofactors for its metabolism has been shown to reduce the risk of cardiovascular events. Information has been emerging regarding a connection between homocysteine metabolism and cognitive function, from mild cognitive decline (age-related memory loss) to vascular dementia and Alzheimer's disease. Significant deficiencies in the homocysteine re-methylation cofactors cobalamin (B12) and folate, as well as the trans-sulfuration cofactor vitamin B6, are commonly seen in

the elderly population, with a resultant increase in homocysteine with advancing age. Hyperhomocysteinemia has been shown to be an independent risk factor for cognitive dysfunction. Indirect and direct vascular damage can be caused by homocysteine, which has been implicated in vascular dementia, with an increased risk of multiple brain infarcts and dementia as homocysteine levels rise. A significant correlation has been found between risk of Alzheimer's disease and high plasma levels of homocysteine, as well as low levels of folic acid, and vitamins B6 and B12. All of these disease associations are thought to be interrelated via increased homocysteine and S-adenosylhomocysteine and subsequent hypomethylation of numerous substances, including DNA and proteins, that render vascular structures and neurons more susceptible to damage and apoptosis. Providing the nutritional cofactors for proper functioning of the methionine cycle may improve methylation and protect the brain from damage. Further studies need to be performed to assess whether this will also reduce the risk of cognitive diseases and/or improve cognitive functioning.

Publication Types:
* Review
* Review Literature

PMID: 12611557 [PubMed - indexed for MEDLINE]

VANADIUM

Vanadium deficiency or imbalance has been associated with bipolar disorder[1,2,3,4,5,6,7,8] and depression[5,9,10].

Vanadium is an essential trace mineral that helps to regulate the circulatory system, prevent excessive cholesterol deposits in blood vessels and cholesterol buildup in the central nervous system, lower elevated blood sugar levels, and is believed to help reduce the incidence of heart attack. In diabetics, vanadium supplements may have a positive effect in regulating blood glucose levels. A normal diet typically provides about 10-30 micrograms (mcg) of vanadium per day from such food sources as seafood, mushrooms, some cereals and soybeans. There is currently no RDA established for vanadium. Vanadium is thought to play a role in metabolism of carbohydrates and may have functions in cholesterol and blood lipid metabolism.

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BORON

Studies have shown a critical role for boron in brain function[1,2,3,4,5].

Boron is nvolved in several important physiological processes, including macro mineral metabolism and the regulation of both the hormones estrogen and testosterone. It is believed to enhance estrogen's role in building bones by helping to convert Vitamin D into the active form necessary for the absorption of calcium. It is therefore essential to bone metabolism and calcification, helping to prevent osteoporosis, arthritis, and tooth decay. Boron is also believed to be necessary for the formation and repair of cartilage. Studies have shown that memory, mental alertness and brain function can be improved with boron. Some research shows that libido can be improved with boron supplementation. Research has also demonstrated boron to be a metabolic regulator and to play an important role in cell membrane function.

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APPENDIX A: RDA AND UL LIMITS

INGREDIENTS	RDA/DAY CHILD 1-3 Y	RDA/DAY CHILD 4-8 Y	UL/DAY CHILD 1-8Y	VITAMIND™ PER CAPSULE	RDA/DAY >9 Y-ADULT	UL/DAY >9 Y-ADULT
Vitamin A	300 µg	400 µg	600-900 µg	300 µg	600-900 µg	1,700-3,000 µg
Vitamin C	15 mg	25 mg	400-650 mg	34 mg	45-120 mg	1,200-2,000 mg
Vitamin D	5 µg	5 µg	50 µg	2.2 µg	5-15 µg	50 µg
Vitamin E	6 mg	7 mg	200-300 mg	14 mg	11-19 mg	600-1,000 mg
Vitamin B1	0.5 mg	0.6 mg	ND	1 mg	0.9-1.4 mg	ND
Vitamin B2	0.5 mg	0.6 mg	ND	0.75 mg	0.9-1.6 mg	ND
Vitamin B3	6 mg	8 mg	10-15 mg	5 mg	12-17 mg	15-35 mg
Vitamin B5	2 mg	3 mg	ND	1.25 mg	4-7 mg	ND
Vitamin B6	0.5 mg	0.6 mg	30-40 mg	2 mg	1-2 mg	60-100 mg
Vitamin B9	150 µg	200 µg	300-400 µg	80 µg	300-500 µg	600-1,000 µg
Vitamin B12	0.9 µg	1.2 µg	ND	50 µg	1.8-2.8 µg	ND
Vitamin H	8 µg	12 µg	ND	50 µg	20-35 µg	ND
Calcium	500 mg	800 mg	2,500 mg	75 mg	1,000-1,300 mg	2,500 mg
Phosphorus	460 mg	500 mg	3,000 mg	46 mg	700-1,250 mg	3,000-4,000 mg
Magnesium	80 mg	130 mg	65-110 mg	34 mg	240-360 mg	350 mg
Potassium	No RDA	No RDA		13 mg	No RDA	
Iodine	90 µg	90 µg	200-300 µg	11 µg	120-290 µg	600-1,100 µg
Zinc	3 mg	5 mg	7-12 mg	2.5 mg	8-13 mg	23-40 mg
Selenium	20 µg	30 µg	90-150 µg	11 µg	40-70 µg	280-400 µg
Copper	340 µg	440 µg	1,000-3,000 µg	400 µg	700-1,300 µg	5,000-10,000 µg
Manganese	1.2 mg	1.5 mg	2-3 mg	0.5 mg	1.9-2.6 mg	6-11 mg
Chromium	11 µg	15 µg	ND	35 µg	25-45 µg	ND
Molybdenum	17 mg	22 mg	300-600 mg	8 ug	34-50 mg	1,100-2,000 mg
Iron	7 mg	10 mg	40 mg	0.75 mg	8-27 mg	40-45 mg
Citrus Bioflavinoids	No RDA	No RDA		60.45 mg		
Grape Seed	No RDA	No RDA				
Choline Bitartrate	200 mg	250 mg	1,000 mg		375-350 mg	2,000-3,500 mg
Inositol	No RDA	No RDA			No RDA	
Ginkgo biloba	No RDA	No RDA			No RDA	
Methionine	No RDA	No RDA			No RDA	
Vanadium	ND	ND	ND		ND	ND
Boron	ND	ND	3-6 mg		ND	11-20 mg

From the USDA Dietary Supplement Guidelines
RDA means recommended daily allowance
UL means upper limit-the maximum value without reported adverse effects
ND means not determinable

APPENDIX B: CENTER FOR SCIENCE IN THE PUBLIC INTEREST: NOV. 10, 2003

FOOD COMPANIES UNDERMINE PARENTS, OVERFEED KIDS

Food marketing aimed at kids undermines parental authority and helps fuel the epidemic of childhood obesity, according to a report issued today by the nonprofit Center for Science in the Public Interest (CSPI). The volume and variety of marketing techniques has exploded, the group says, as food marketers seek new ways of bypassing parents and directly influencing kids' food choices. Regrettably, most of the foods marketed directly to children are high in calories and low in nutrition, the group says.

"Parents are fighting a losing battle against food manufacturers and fast-food restaurants, which use aggressive and sophisticated techniques to get into children's heads and prompt them to pester their parents to purchase the company's products," said Margo G. Wootan, director of nutrition policy at CSPI and the report's author. "SpongeBob Squarepants, Winnie the Pooh, Elmo, and even sports stars like Jason Giambi are enlisted to push low-nutrition foods on kids."

The CSPI report identifies a plethora of ways that companies target kids in their homes, in their schools, on the web, and wherever else kids go. Examples highlighted in the report include:

- Campbell's "Labels for Education" program encourages families to collect labels from Campbell products that schools can redeem for equipment. It's hardly model philanthropy, says CSPI, seeing that kids' parents would have to buy some $2,500 worth of soup , for the school to qualify for a $59 stapler.

- Krispy Kreme "Good Grades" program offers elementary school kids one doughnut for each "A" on their report cards. CSPI points out that some states wisely prohibit or discourage using food as a reward for good behaviour or academic performance.

- McDonald's Barbie has the doll dressed up as a McDonald's clerk, feeding French fries, burgers, and Sprite to kid-sister Kelly in a restaurant playset. "Unless McDonald's is paying you for ad space in the playroom, leave this toy at the store," Wootan said. Same goes, she says for other junk-food ads disguised as toys, like Play Doh's Lunchables kit, where kids are encouraged to assemble Play Doh versions of Oscar Mayer's notoriously fatty and salty lunch box items.

- The Oreo Adventure game on Kraft Foods' Nabiscoworld.com web site is one of many corporate "advergames". In this video game, children's "health" is reset to "100 percent" when kids acquire golden cookie jars on a journey to a Temple of the Golden Oreo. The Oreo Matchin' Middles shape-matching game, produced with Fisher Price, turns playtime into a chance for companies to cultivate brand loyalty and sell junk food.

- Pepsi's website profile of New York Yankees baseball star Jason Giambi, which prominently displays the quote, "I usually have several Pepsis each day—it

really lifts me up," is one of many examples of a junk-food marketer linking consumption of its product with fitness.

- Cap'n Crunch Smashed Berries cereal—which, predictably, has no berries at all—encourages overeating in its magazine advertisements. Once such ad in Nickelodeon magazine reads, "Kids smashed 'em in the factory so you can fit more in your mouth."

"No amount of eye-rolling can capture how hypocritical it is for food company flacks to talk about 'moderation, balance, and exercise," said CSPI executive director Michael F. Jacobson. "Anyone who looks at these marketing techniques can see that they encourage excess, not moderation. Almost exclusively, they encourage consumption an unbalanced diet of high-cal and low-nutrient foods. And to link junk foods like Oreos or Pepsi to physical fitness or athletic prowess has to be one of the most cynical and unfair marketing strategies I've ever seen."

In the 1970s and 1980s, the Federal Trade Commission considered restrictions on junk-food advertising aimed at kids, but those efforts were blocked by food, toy, broadcasting, and advertising industries. CSPI says that with rates of obesity at all-time highs in children, now is the time to set standards on what foods may be marketed to kids on television and in schools. CSPI also recommends that governments sponsor media campaigns that encourage healthy eating and physical activity, and that grocers put low-nutrition foods at parents' eye level, not kids' eye level.

CSPI encourages state and local governments to fund their own nutrition media campaigns by earmarking or increasing taxes on soft drinks. More than a dozen states already have such taxes, though their revenues typically go into general funds, and are not spent promoting good nutrition or exercise.

Today, CSPI also called on Secretary of Health and Human Services Tommy Thompson to make the issue of marketing junk food to kids a central focus of the administration's anti-obesity campaign.

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APPENDIX C

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