

## Basically Better™ Product Science–Vitamin/Micronutrient Abstracts

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### **Vitamin D: New Way To Treat Heart Failure?**

ScienceDaily (Jun. 12, 2008) — Strong bones, a healthy immune system, protection against some types of cancer: Recent studies suggest there's yet another item for the expanding list of Vitamin D benefits. Vitamin D, "the sunshine vitamin," keeps the heart, the body's long-distance runner, fit for life's demands.

University of Michigan pharmacologist Robert U. Simpson, Ph.D., thinks it's apt to call vitamin D "the heart tranquilizer."

In studies in rats, Simpson and his team report the first concrete evidence that treatment with activated vitamin D can protect against heart failure. Their results appear in the July issue of the Journal of Cardiovascular Pharmacology.

In the study, treatments with activated vitamin D prevented heart muscle cells from growing bigger – the condition, called hypertrophy, in which the heart becomes enlarged and overworked in people with heart failure. The treatments prevented heart muscle cells from the over-stimulation and increased contractions associated with the progression of heart failure.

About 5.3 million Americans have heart failure, a progressive, disabling condition in which the heart becomes enlarged as it is forced to work harder and harder, making it a challenge even to perform normal daily activities. Many people with heart disease or poorly controlled high blood pressure go on to experience a form of heart failure called congestive heart failure, in which the heart's inability to pump blood around the body causes weakness and fluid build-up in lungs and limbs. Many people with heart

failure, who tend to be older, have been found to be deficient in vitamin D.

"Heart failure will progress despite the best medications," says Simpson, a professor of pharmacology at the U-M Medical School. "We think vitamin D retards that progression and protects the heart."

The U-M researchers wanted to show whether a form of vitamin D could have beneficial effects on hearts that have developed or are at risk of developing heart failure. They used a breed of laboratory rats predisposed to develop human-like heart failure.

The researchers measured the effects of activated Vitamin D (1,25 dihydroxyvitamin D<sub>3</sub>, a form called calcitriol) in rats given a normal diet or a high-salt diet, compared to control group rats given either of the same two diets, but no vitamin D treatment. The rats on the high-salt diet were likely to develop heart failure within months.

The rats on the high-salt diet, comparable to the fast food that many humans feast on, quickly revealed the difference vitamin D could make.

"From these animals, we have obtained exciting and very important results," Simpson says.

After 13 weeks, the researchers found that the heart failure-prone rats on the high-salt diet that were given the calcitriol treatment had significantly lower levels of several key indicators of heart failure than the untreated high-salt diet rats in the study. The treated rats had lower heart weight. Also, the left ventricles of the treated rats' hearts were smaller and their hearts worked less for each beat while blood pressure was maintained, indicating that their heart function did not deteriorate as it did in the untreated rats. Decreased heart weight, meaning that enlargement was not occurring, also showed up in the treated rats fed a normal diet, compared to their untreated counterparts.

Simpson and his colleagues have explored vitamin D's effects on heart muscle and the cardiovascular system for more than 20 years. In 1987, when Simpson showed the link between vitamin D and heart health, the idea seemed far-fetched and research funding was scarce. Now, a number of studies worldwide attest to the vitamin D-heart health link (see citations below).

The new heart insights add to the growing awareness that widespread vitamin D deficiency—thought to affect one-third to one-half of U.S. adults middle-aged and older—may be putting people at greater risk of many common diseases. Pharmaceutical companies are developing anti-cancer drugs using vitamin D analogs, which are synthetic compounds that produce vitamin D's effects. There's also increasing interest in using vitamin D or its analogs to treat autoimmune disorders.

In more than a dozen types of tissues and cells in the body, activated vitamin D acts as a powerful hormone, regulating expression of essential genes and rapidly activating already expressed enzymes and proteins. In the heart, Simpson's team has revealed precisely how activated vitamin D connects with specific vitamin D receptors and produces its calming, protective effects. Those results appeared in the February issue of Endocrinology.

Sunlight causes the skin to make activated vitamin D. People also get vitamin D from certain foods and vitamin D supplements. Taking vitamin D supplements and for many people, getting sun exposure in safe ways, are certainly good options for people who want to keep their hearts healthy. But people with heart failure or at risk of heart failure will likely need a drug made of a compound or analog of vitamin D that will more powerfully produce vitamin D's effects in the heart if they are to see improvement in their symptoms, Simpson says.

Vitamin D analogs already are on the market for some conditions. One present drawback of these compounds is that they tend to increase blood calcium to undesirable levels. Simpson's lab is conducting studies of a specific analog which may be less toxic, so efforts to develop a vitamin D-based drug

to treat heart failure are moving a step closer to initial trials in people.

In addition to Simpson, other U-M authors include Peter Mancuso, Ph.D., of the U-M Department of Environmental Health Sciences; Ayesha Rahman, Ph.D., Stephen D. Hershey, M.D., Loredana Dandu and Karl A. Nibbelink, M.D. of the Department of Pharmacology in the U-M Medical School.

Funding for the study came from the National Institutes of University of Michigan Health System (2008, June 12). *Vitamin D: New Way To Treat Heart Failure?*. *ScienceDaily*. Retrieved June 12, 2008,

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## **Trends Of Vitamin B6 Status In US Population Sample Identified**

*ScienceDaily* (May 23, 2008) — In an epidemiological study, Tufts University researchers identified trends of vitamin B6 status in a sample of the United States population based on measures of plasma pyridoxal 5'-phosphate (PLP) levels in the bloodstream. Plasma PLP is the indicator used by the federal government to set the current Recommended Dietary Allowance (RDA) of vitamin B6, a nutrient essential for red blood cell function and important for maintaining a healthy immune system and blood glucose levels.

"Across the study population, we noticed participants with inadequate vitamin B6 status even though they reported consuming more than the Recommended Daily Allowance of vitamin B6, which is less than 2 milligrams per day," says Martha Savaria Morris, PhD, an epidemiologist at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. "We also identified four subgroups where this trend seemed most prominent: women of reproductive age, especially current and former users of oral contraceptives, male smokers, non-Hispanic African-American men, and men and women over age 65." Someone with inadequate vitamin B6 status is at risk of

becoming Vitamin B6 deficient should their vitamin B6 levels drop too low.

Corresponding author Morris and colleagues studied 7,822 blood samples of men and women ages one-year and older collected from the 2003-2004 National Health and Nutrition Examination Survey (NHANES). Vitamin B6 inadequacy was defined as a plasma PLP concentration less than 20 nmol/L. To the authors' knowledge, the current study is the first large scale study to use plasma PLP concentrations to evaluate vitamin B6 status in free-living people of all ages. The investigators were also able to consider whether the current RDA guaranteed adequate vitamin B6 status because study participants were questioned about supplement use and two days' worth of food intake.

Eleven percent of supplement users and nearly a quarter of non-users demonstrated plasma PLP blood levels of less than 20 nmol/L. Within the four sub-groups where vitamin B6 inadequacy was most prominent, the prevalence of low plasma PLP levels significantly exceeded 10 percent—even among those who consumed 2 to 2.9 milligrams per day of vitamin B6. The RDAs for vitamin B6 in men and women who are not pregnant or lactating are as follows: 1.3 mg per day for men and women ages 19-50, 1.7 mg per day for men over age 50 and 1.5 mg for women over age 50.

Morris and colleagues noted a stark contrast in plasma PLP levels between women of childbearing age (ages 13 to 54) and their male peers. "When we looked specifically at the plasma PLP levels in women of childbearing age, we noticed they were significantly lower than in males in approximately the same age group." Morris continues, "Most importantly, **the data suggest that oral contraceptive users have extremely low plasma PLP levels.** Three quarters of the women who reported using oral contraceptives, but not vitamin B6 supplements, were vitamin B6 deficient."

A pattern of low vitamin B6 status also surfaced in menstruating women who reported using oral contraceptives but who were no longer using them at the time of the NHANES survey. Among

women in this sub-group who were not taking vitamin B6 supplements, 40 percent demonstrated plasma PLP blood levels below the cut-off for vitamin B6 inadequacy. Morris says, that although these results are somewhat surprising, the link between oral contraceptive use and vitamin B6 deficiency remains unclear. "The vitamin could be stored elsewhere in the bodies of the oral contraceptive users, or in a different form, since our study only examined plasma PLP."

To further support their findings, Morris and colleagues measured homocysteine levels in the blood and compared them against the plasma PLP measures. Homocysteine is an amino acid that can accumulate in the blood if vitamin B6 levels are too low. Though study participants using oral contraceptives at the time of the survey did not demonstrate elevated homocysteine levels, the homocysteine concentrations of former users were significantly higher than those of women who had never used oral contraceptives. Morris says this could mean that oral contraceptive use has an effect on vitamin B6 status that is masked during use by acute effects of the exposure.

Because the study shows association and not causation, Morris stresses that further research is necessary to determine whether the RDA for vitamin B6 is high enough. "We have identified populations with a high prevalence of apparently inadequate vitamin B status," Morris says. "However, it is important to recognize that signs of deficiency are not seen at plasma PLP concentrations of 20 nmol/L and that dietary assessment is imperfect."

According to the National Institutes of Health (NIH), vitamin B6 deficiency is rare in the United States, but it can cause a form of anemia similar to iron deficiency anemia. Vitamin B6 is widely distributed in the American diet, and baked potatoes, bananas, 100 percent fortified cereals and chicken are particularly good sources. Morris says, "The question our study raises is whether, due to aging, genetics, or exposures, some population subgroups need supplements to achieve the current biochemical definition of adequate status."

This study was supported by the National Institutes of Health and by the U.S. Department of Agriculture.

**Journal reference:** Morris MS, Picciano, MF, Jacques PF, Selhub, J. American Journal of Clinical Nutrition. 2008 (May); 87: 1446-54.

Tufts University, Health Sciences (2008, May 23). Trends Of Vitamin B6 Status In US Population Sample Identified. *ScienceDaily*. Retrieved May 23, 2008

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### **Vitamin D Protects Cells From Stress That Can Lead To Cancer**

*ScienceDaily* (May 13, 2008) — By inducing a specific gene to increase expression of a key enzyme, vitamin D protects healthy prostate cells from the damage and injuries that can lead to cancer, University of Rochester Medical Center researchers report.

"Many epidemiological studies have suggested the beneficial properties of vitamin D," said Yi-Fen Lee, associate professor of urology at the Medical Center who led the research. "Our findings reflect what we see in those studies and demonstrate that vitamin D not only can be used as a therapy for prostate cancer, it can prevent prostate cancer from happening."

The International Journal of Cancer published the findings in its June 15 issue.

Lee and her research team discovered one mechanism involving vitamin D that protects cells from oxidative stress. The vitamin D used in the study is 1,25-hydroxylvitamin D3, the most potent and active form of vitamin D in the human body. Nonmalignant human prostate epithelial cells also were used.

Normal metabolism in cells generates reactive oxygen species (ROS), molecules of peroxide, for example, or so-called free

radicals. These substances can play a role in cell signaling and even kill bacteria. Exposure to some chemicals or forms of radiation can produce high levels of ROS that can damage DNA and play a significant role in speeding aging or causing cancer.

Lee found that vitamin D links with a gene known as G6PD, increasing its activity and the production of an enzyme called glucose-6-phosphate dehydrogenase. Increased activity of the enzyme clears cells of ROS, the molecules that can damage and injure cells.

"If you reduce DNA damage, you reduce the risk of cancer or aging," Lee said. "Our study adds one more beneficial effect of taking a vitamin D supplement. Taking a supplement is especially important for senior citizens and others who might have less circulation of vitamin D, and for people who live and work areas where there is less sunshine."

Large amounts of vitamin D should not be taken without medical supervision, she said.

The G6PD pathway is one of the mechanisms vitamin D uses, Lee said. The researchers did not find any similar activity in prostate cancer cells.

"Vitamin D does not protect cancer cells from injury or damage, which is good," Lee said.

The current research was supported by a grant from the U.S. Department of Defense.

In addition to Lee, authors of the International Journal of Cancer article include Bo-Ying Bao of China Medical University, Taichung, Taiwan, and Huei-Ju Ting and Jong-Wei Hsu of the Medical Center.

In the journal Carcinogenesis in 2006, Lee reported that vitamin D can inhibit the spread of prostate cancer by limiting the ability of cancer cells to invade healthy cells by reducing the activity of two specific enzymes, proteases called matrix metalloproteinase

and cathepsin. The research was conducted in test tubes using human prostate cancer cell lines. That finding indicated that vitamin D could provide beneficial treatment to prostate cancer patients with high levels of the enzymes.

University of Rochester Medical Center (2008, May 13). *Vitamin D Protects Cells From Stress That Can Lead To Cancer.* *ScienceDaily*. Retrieved May 14, 2008

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### **Vitamin D Important In Brain Development And Function**

*ScienceDaily* (Apr. 23, 2008) — In a definitive critical review, scientists at Children's Hospital & Research Center Oakland ask whether there is convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction. Joyce C. McCann, Ph.D., assistant staff scientist and Bruce N. Ames, Ph.D., senior scientist at Children's Hospital Oakland Research Institute (CHORI) conclude that there is ample biological evidence to suggest an important role for vitamin D in brain development and function, and that supplementation for groups chronically low in vitamin D is warranted. Their conclusions will be published on April 22, 2008 in the Federation of American Societies for Experimental Biology (FASEB) Journal.

"This critical analysis of vitamin D function and the brain is a model of careful thinking about nutrition and behavior", says Gerald Weissmann, MD, Editor-in-Chief of the FASEB Journal "One wishes that all studies of nutritional supplements or requirements were this thoughtful. Drs. McCann and Ames deftly show that while vitamin D has an important role in the development and function of the brain, its exact effects on behavior remain unclear. Pointing to the need for further study, the authors argue for vitamin D supplementation in groups at risk."

Vitamin D has long been known to promote healthy bones by regulating calcium levels in the body. Lack of sufficient vitamin D

in very young children results in rickets, which can be easily prevented by vitamin D supplements. Only recently the scientific community has become aware of a much broader role for vitamin D. For example, we now know that, in addition to its role in maintaining bone health, vitamin D is involved in differentiation of tissues during development and in proper functioning of the immune system.

In fact, over 900 different genes are now known to be able to bind the vitamin D receptor, through which vitamin D mediates its effects. In addition to protecting against rickets, evidence now strongly indicates that a plentiful supply of vitamin D helps to protect against bone fractures in the elderly. Evidence also continues to accumulate suggesting a beneficial role for vitamin D in protecting against autoimmune diseases, including multiple sclerosis and type I diabetes, as well as some forms of cancer, particularly colorectal and breast.

Vitamin D is present in only a few foods (e.g., fatty fish), and is also added to fortified milk, but our supply typically comes mostly from exposure to ultraviolet rays (UV) in sunlight. UV from the sun converts a biochemical in the skin to vitamin D, which is then metabolized to calcitriol, its active form and an important hormone. Formation of vitamin D by UV can be 6 times more efficient in light skin than dark skin, which is an important cause of the known widespread vitamin D deficiency among African Americans living in northern latitudes. Dark skin has been selected during evolution because it protects against the burning UV rays of the sun in the tropics.

White skin has been selected for allowing as much UV exposure to make sufficient vitamin D in Northern (high) latitudes. Thus, fair-skinned northerners are at risk in Australia or Arizona for sunburns and UV-induced cancer, while dark-skinned people in the Northern U.S. or European latitudes with little exposure to the sun are at risk for rickets, bone fractures and possibly other diseases including several types of cancer due to a lack of vitamin D. Fortunately sun-screens and vitamin D supplements are inexpensive.

McCann & Ames point out that evidence for vitamin D's involvement in brain function includes the wide distribution of vitamin D receptors throughout the brain. They also discuss vitamin D's ability to affect proteins in the brain known to be directly involved in learning and memory, motor control, and possibly even maternal and social behavior. The review also discusses studies in both humans and animals that present suggestive though not definitive evidence of cognitive or behavioral consequences of vitamin D inadequacy. The authors discuss possible reasons for the apparent discrepancy between the biological and behavioral evidence, and suggest new, possibly clarifying avenues of research.

Many vitamin D experts advise that the currently recommended level of vitamin D intake is much too low and should be raised to protect against bone fractures and possibly cancer in addition to rickets (2). Indeed, even using present guidelines, too many Americans have low vitamin D blood levels. McCann & Ames propose that, despite uncertainty regarding all of the deleterious effects of vitamin D inadequacy, the evidence overall indicates that supplementation, which is both inexpensive and prudent, is warranted for groups whose vitamin D status is exceptionally low, particularly nursing infants, the elderly, and African Americans (e.g., see (3)).

This review is the fourth in a series by McCann & Ames that critically evaluate scientific evidence linking deficiencies in micronutrients (the approximately 40 vitamins, minerals, amino acids, and fatty acids required for the body to function) to brain function. Other reviews in the series discuss the long-chain polyunsaturated fatty acid docosahexaenoic acid (DHA) (4, 5), choline (6), and iron (7).

## References

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Children's Hospital & Research Center at Oakland (2008, April 23). Vitamin D Important In Brain Development And Function. *ScienceDaily*. Retrieved April 23, 2008

(5)

### **A Ray Of Sunshine In The Fight Against Cancer: Vitamin D May Help**

*ScienceDaily* (Feb. 16, 2008) — It sounds too good to be true ... a little inexpensive pill that could block the development of some cancers, strengthen bones, prevent multiple sclerosis and alleviate winter depression.

But it's not science fiction. The "new aspirin" could be Vitamin D. Just as we discovered that aspirin can guard against heart disease, Vitamin D could become a useful weapon in the fight against MS, osteoporosis, mild depression and one of the most devastating diseases of our time – cancer.

"As time has gone by, Vitamin D has raised its head as a sort of ambrosia for cancers," says Dr. Louise Parker, an epidemiologist and a world expert in the environmental exposures that can lead to cancer. Or, in the case of Vitamin D, the lack of exposure.

"One of the most important sources of Vitamin D is from the sun and through your skin," says Dr. Parker.

"Many parts of Canada don't get much sun in the winter. We've also been telling people to cover up and use sunscreen to prevent skin cancer. Sunscreen actually impairs your (skin's ability) to make Vitamin D."

So the Canadian Cancer Society recommends that during the winter, Canadians take at least 1,000 units a day of Vitamin D, dubbed "the sunshine vitamin."

Dr. Parker says 1,000 units a day is well beyond what you can obtain from your diet. Vitamin D is a bit of a rare vitamin, appearing only in fatty fish, cod liver oil and egg yolks. Even if you were to sunbathe in southern climates, you would not take in 1,000 units.

"If you were to lie naked on a beach in the Bahamas, and I don't recommend that because of skin cancer, you cannot get up to the equivalent of 1,000 units of Vitamin D a day," says Dr. Parker.

She notes Vitamin D as a factor is turning up in study after study. It turns out people with lung and colon cancer are Vitamin D deficient. And it helps the body absorb calcium. In a study examining whether women who took Vitamin D had a lower risk of osteoporosis, it was found the women taking Vitamin D had stronger bones than those who did not take the vitamin. Years later, researchers went back to that study and found that the women who took Vitamin D also had fewer cancers.

But before Vitamin D becomes the "new aspirin," more research needs to be carried out.

Vitamin D works in very complicated ways, she says. It changes the way cells work. In fact, there is medical speculation that it

may block cancer cell proliferation or improve immune system functions. But its role is not fully understood.

Lifestyle also has to be part of the equation. Dr. Parker is looking at how obesity, which we know can cause cancer, and exercise, which we know prevents cancer, could interact with Vitamin D. "At the population level, I am trying to understand how all these things fit together," says Dr. Parker. "It's very complex." Dr. Parker describes it as looking for a piece of a jigsaw puzzle. "We know some of the jigsaw pieces, but not all," she says.

Meanwhile, there is very little evidence that taking Vitamin D can harm you. Perhaps in huge doses it could cause kidney stones, but that has not been proven.

"On the average, 1,000 units a day is safe and is probably effective in reducing the risk of colon cancer, and maybe other cancers as well," says Dr. Parker.

So does she take Vitamin D and recommend it? Absolutely. "I take 1,000 units of Vitamin D – one day on and one day off," she says.

Dalhousie University (2008, February 16). *A Ray Of Sunshine In The Fight Against Cancer: Vitamin D May Help*. ScienceDaily. Retrieved February 17, 2008

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[Evid Rep Technol Assess \(Full Rep\)](#). 2006 May;(139):1-117.

### **Multivitamin/mineral supplements and prevention of chronic disease.**

**Huang HY, Caballero B, Chang S, Alberg A, Semba R, Schneyer C, Wilson RF, Cheng TY, Prokopowicz G, Barnes GJ 2nd, Vassy J, Bass EB.**

OBJECTIVES: To review and synthesize published literature on the efficacy of multivitamin/mineral supplements and certain single nutrient supplements in the primary prevention of chronic disease in the general adult population, and on the safety of multivitamin/mineral supplements and certain single nutrient supplements, likely to be included in multivitamin/mineral supplements, in the general population of adults and children.

DATA SOURCES: All articles published through February 28, 2006, on MEDLINE, EMBASE, and the Cochrane databases. REVIEW METHODS: Each article underwent double reviews on title, abstract, and inclusion eligibility. Two reviewers performed data abstraction and quality assessment. Differences in opinion were resolved through consensus adjudication. RESULTS: Few trials have addressed the efficacy of multivitamin/mineral supplement use in chronic disease prevention in the general population of the United States. One trial on poorly nourished Chinese showed supplementation with combined Beta-carotene, vitamin E and selenium reduced gastric cancer incidence and mortality, and overall cancer mortality. In a French trial, combined vitamin C, vitamin E, Beta-carotene, selenium, and zinc reduced cancer risk in men but not in women. No cardiovascular benefit was evident in both trials. Multivitamin/mineral supplement use had no benefit for preventing cataract. Zinc/antioxidants had benefits for preventing advanced age-related macular degeneration in persons at high risk for the disease. With few exceptions, neither Beta-carotene nor vitamin E had benefits for preventing cancer, cardiovascular disease, cataract, and age-related macular degeneration. Beta-carotene supplementation increased lung cancer risk in smokers and persons exposed to asbestos. Folic acid alone or combined with vitamin B12 and/or vitamin B6 had no significant effects on cognitive function. Selenium may confer benefit for cancer prevention but not cardiovascular disease prevention. Calcium may prevent bone mineral density loss in postmenopausal women, and may reduce vertebral fractures, but not non-vertebral fractures. The evidence suggests dose-dependent benefits of vitamin D with/without calcium for retaining bone mineral density and preventing hip fracture, non-vertebral fracture and falls. We found no consistent pattern of increased adverse effects of multivitamin/mineral supplements except for skin yellowing by Beta-carotene. CONCLUSIONS: Multivitamin/mineral supplement use may prevent cancer in individuals with poor or suboptimal nutritional status. The heterogeneity in the study populations limits generalization to United States population. Multivitamin/mineral supplements conferred no benefit in preventing cardiovascular disease or cataract, and may prevent advanced age-related macular degeneration only in high-risk individuals. The overall quality and

quantity of the literature on the safety of multivitamin/mineral supplements is limited.

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