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<http://www.mayoclinic.org/news2009-rst/5532.html>

Mayo Clinic and Collaborators Find Vitamin D Levels are Associated with Survival in Lymphoma Patients

Saturday, December 05, 2009

ROCHESTER, Minn. — A new study has found that the amount of vitamin D in patients being treated for diffuse large B-cell lymphoma was strongly associated with cancer progression and overall survival. The results will be presented at the annual meeting of the American Society of Hematology in New Orleans.

VIDEO ALERT: Additional audio and video resources including excerpts from an interview with Dr. Matthew Drake describing the research are available on the Mayo Clinic News Blog. These materials are also subject to embargo, but may be accessed in advance by journalist for incorporation into stories. The password for this post is: drake12.

"These are some of the strongest findings yet between vitamin D and cancer outcome," says the study's lead investigator, Matthew Drake, M.D., Ph.D., an endocrinologist at Mayo Clinic in Rochester. "While these findings are very provocative, they are preliminary and need to be validated in other studies. However, they raise the issue of whether vitamin D supplementation might aid in treatment for this malignancy, and thus should stimulate much more research."

The researchers' study of 374 newly diagnosed diffuse large B-cell lymphoma patients found that 50 percent had deficient vitamin D levels based on the commonly used clinical value of total serum 25(OH)D less than 25 ng/mL. Patients with deficient vitamin D levels had a 1.5-fold greater risk of disease progression and a twofold greater risk of dying, compared to patients with optimal vitamin D levels after accounting for other patient factors associated with worse outcomes.

The study was conducted by a team of researchers from Mayo Clinic and the University of Iowa. These researchers participate in the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE), which is funded by the National Cancer Institute. The 374 patients were enrolled in an epidemiologic study designed to identify predictors of outcomes in lymphoma. Since this was not a clinical trial, patient management and treatments were not assigned, but rather followed standard of care for clinical practice.

The findings support the growing association between vitamin D and cancer risk and outcomes, and suggest that vitamin D supplements might help even those patients already diagnosed with some forms of cancer, says Dr. Drake. "The exact roles that vitamin D might play in the initiation or progression of cancer is unknown, but we do know that the vitamin plays a role in regulation of cell growth and death, among other processes important in limiting cancer," he says.

The findings also reinforce research in other fields that suggest vitamin D is important to general health, Dr. Drake says. "It is fairly easy to maintain vitamin D levels through inexpensive daily supplements or 15 minutes in the sun three times a week in the summer, so that levels can be stored inside body fat," he says. Many physicians recommend 800-1,200 International Units (IU) daily, he adds.

Vitamin D is a steroid hormone obtained from sunlight and converted by the skin into its active form. It also can come from food (naturally or fortified as in milk) or from supplements. It is known best for its role of increasing the flow of calcium into the blood. Because of that role, vitamin D deficiency has long been known to be a major risk factor for bone loss and bone fractures, particularly in elderly people whose skin is less efficient at converting sunlight into vitamin D. But recent research has found that many people suffer from the deficiency, and investigators are actively looking at whether low vitamin D promotes poorer health in general.

Cancer researchers have discovered that vitamin D regulates a number of genes in various cancers, including prostate, colon and breast cancers. Recent studies have suggested that vitamin D deficiency may play a role in causing certain cancers as well as impacting the outcome once someone is diagnosed with cancer.

Researchers looked at vitamin D levels in lymphoma patients because of the observation, culled from U.S. mortality maps issued by the National Cancer Institute, that both incidence and mortality rates of this cancer increase the farther north a person lives in the United States, where sunlight is limited in the winter. Also, several recent reports have concluded that vitamin D deficiency is associated with poor outcomes in other cancers, including breast, colon and head and neck cancer. This is the first study to look at lymphoma outcome.

The study was funded by the National Cancer Institute and the Mayo Hematologic Malignancies Lymphoma Fund.

Other members of the Mayo research team include Ivana Micallef, M.D.; Thomas Habermann, M.D.; William Macon, M.D.; Joseph Colgan, M.D.; Matthew Maurer; Cristine Allmer; Susan Slager, Ph.D.; Thomas Witzig, M.D., and James Cerhan, M.D., Ph.D. Additional researchers include Brian Link, M.D., and George Weiner, M.D., both

from the University of Iowa, Iowa City; Jennifer Kelly, Ph.D., University of Rochester in Rochester, N.Y.; and Daniel Nikcevich, M.D., St. Mary's Duluth Clinic, Duluth, Minn.

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Opioid receptors control the metabolic response to a high-energy diet in mice

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ESSENCE OF ARTICLE

." This study provides the first evidence that KORs play an essential physiological role in the control of hepatic lipid metabolism, and KOR activation is a permissive signal toward fat storage".—

ARTICLE

General opioid receptor antagonists reduce food intake and body weight in rodents, but the contributions of specific receptor subtypes are unknown. We examined whether genetic deletion of the μ -opioid receptor (KOR) in mice alters metabolic physiology. KOR-knockout (KO) and wild-type (WT) mice were fed a high-energy diet (HED) for 16 wk. KO mice had 28% lower body weight and 45% lower fat mass when compared to WT mice fed an HED. No differences in caloric intake were found. An HED reduced energy expenditure in WT mice, but not in KO mice. KOR deficiency led to an attenuation of triglyceride synthesis in the liver. Malonyl CoA levels were also reduced in response to an HED, thereby promoting hepatic β -oxidation. Glycemic control was also found to be improved in KO mice. These data suggest a key role for KORs in the central nervous system regulation of the metabolic adaptation to an HED, as we were unable to detect expression of KOR in liver, white adipose tissue, or skeletal muscle in WT mice. This study provides the first evidence that KORs play an essential physiological role in the control of hepatic lipid metabolism, and KOR activation is a permissive signal toward fat storage.—Czyzyk, T. A., Nogueiras, R., Lockwood, J. F., McKinzie, J. H., Coskun, T., Pintar, J. E., Hammond, C., Tschöp, M. H., Statnick, M. A. μ -Opioid receptors control the metabolic response to a high-energy diet in mice.

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Federation of American Societies for Experimental Biology

New research in the FASEB Journal suggests that highly palatable, energy-dense foods may activate genes that ultimately make us obese

Those extra helpings of gravy and dessert at the holiday table are even less of a help to your waistline than previously thought. According to a new research report recently appearing online in The FASEB Journal (<http://www.fasebj.org>), a diet that is high in fat and in sugar actually switches on genes that ultimately cause our bodies to store too much fat. This means these foods hit you with a double-whammy as the already difficult task of converting high-fat and high-sugar foods to energy is made even harder because these foods also turn our bodies into "supersized fat-storing" machines.

In the research report, scientists show that foods high in fat and sugar stimulate a known opioid receptor, called the kappa opioid receptor, which plays a role in fat metabolism. When this receptor is stimulated, it causes our bodies to hold on to far more fat than our bodies would do otherwise.

According to Traci Ann Czyzyk-Morgan, one of the researchers involved in the work, "the data presented here support the hypothesis that overactivation of kappa opioid receptors contribute to the development of obesity specifically during prolonged consumption of high-fat, calorically dense diets."

To make this discovery, Czyzyk-Morgan and her colleagues conducted tests in two groups of mice. One group had the kappa opioid receptor genetically deactivated ("knocked out") and the other group was normal. Both groups were given a high fat, high sucrose, energy dense diet for 16 weeks. While the control group of mice gained significant weight and fat mass on this diet, the mice with the deactivated receptor remained lean. In addition to

having reduced fat stores, the mice with the deactivated receptor also showed a reduced ability to store incoming nutrients.

Although more work is necessary to examine what the exact effects would be in humans, this research may help address the growing obesity problem worldwide in both the short-term and long-term. Most immediately, this research provides more proof that high-fat and high-sugar diets should be avoided. In the long-term, however, this research is even more significant, as it provides a new drug target for developing therapies for preventing obesity and helping obese people slim down.

"In times when food was scarce and starvation an ever-present threat, an adaptation that allows our bodies to store as much energy as possible during plentiful times was probably a lifesaver," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "By taking that opioid receptor off the table, researchers may have found a way to keep us from eating ourselves to death."

Receive monthly highlights from The FASEB Journal by e-mail. Sign up at <http://www.faseb.org/fasebjournalreaders.htm>. The FASEB Journal (<http://www.fasebj.org>) is published by the Federation of the American Societies for Experimental Biology (FASEB). The journal has been recognized by the Special Libraries Association as one of the top 100 most influential biomedical journals of the past century and is the most cited biology journal worldwide according to the Institute for Scientific Information. FASEB comprises 22 nonprofit societies with more than 80,000 members, making it the largest coalition of biomedical research associations in the United States. FASEB advances biological science through collaborative advocacy for research policies that promote scientific progress and education and lead to improvements in human health.

Details: Traci A. Czyzyk, Ruben Nogueiras, John F. Lockwood, Jamie H. McKinzie, Tamer Coskun, John E. Pintar, Craig Hammond, Matthias H. Tschöp, and Michael A. Statnick -Opioid receptors control the metabolic response to a high-energy diet in mice. FASEB J. doi:10.1096/fj.09-143610 ; <http://www.fasebj.org/cgi/content/abstract/fj.09-143610v1>

<http://scielinks.jp/j-east/article/200302/000020030202A0869635.php>

CJ-15,208, a Novel Kappa Opioid Receptor Antagonist from a Fungus, *Ctenomyces serratus* ATCC15502.

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ESSENCE OF ARTICLE IS WHOLE ARTICLE

Abstract;A novel .KAPPA. opioid receptor binding inhibitor CJ-15,208 (I) was isolated from the fermentation broth of a fungus, *Ctenomyces serratus* ATCC15502. The structure of I was determined to be a cyclic tetrapeptide consisting of one tryptophan, one D-proline, and two L-phenylalanine. Compound I was a selective binding inhibitor for the .KAPPA. opioid receptor: 47 nM (IC₅₀) for .KAPPA., 260 nM for .MU., and 2,600 nM for .DELTA.. In the electrically-stimulated twitch response assay of rabbit *vas deferens* I recovered the suppression by a .KAPPA. agonist *asimadoline* with an ED₅₀ of 1.3 .MU.M, indicating that it is a .KAPPA. antagonist. (author abst.)

<http://jcem.endojournals.org/cgi/content/abstract/87/4/1687>

Selenium Supplementation in Patients with Autoimmune Thyroiditis Decreases Thyroid Peroxidase Antibodies Concentrations

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ESSENCE OF ARTICLE

"We conclude that selenium substitution may improve the inflammatory activity in patients with autoimmune thyroiditis, especially in those with high activity. Whether this effect is specific for autoimmune thyroiditis or may also be effective in other endocrine autoimmune diseases has yet to be investigated. "

ARTICLE

Abstract

In areas with severe selenium deficiency there is a higher incidence of thyroiditis due to a decreased activity of selenium-dependent glutathione peroxidase activity within thyroid cells. Selenium-dependent enzymes also have several modifying effects on the immune system. Therefore, even mild selenium deficiency may contribute to the development and maintenance of autoimmune thyroid diseases. We performed a blinded, placebo-controlled, prospective study in female patients (n = 70; mean age, 47.5 ± 0.7 yr) with autoimmune thyroiditis and thyroid peroxidase antibodies (TPOAb) and/or Tg antibodies (TgAb) above 350 IU/ml. The primary end point of the study was the change in TPOAb concentrations. Secondary end points were changes in TgAb, TSH, and free thyroid hormone levels as well as ultrasound pattern of the thyroid and quality of life estimation. Patients were randomized into 2 age- and antibody (TPOAb)-matched groups; 36 patients received 200 µg (2.53 µmol) sodium selenite/d, orally, for 3 months, and 34 patients received placebo. All patients were substituted with L-T₄ to maintain TSH within the normal range. TPOAb, TgAb, TSH, and free thyroid hormones were determined by commercial assays. The echogenicity of the thyroid was monitored with high resolution ultrasound. The mean TPOAb concentration decreased significantly to 63.6% (P = 0.013) in the selenium group vs. 88% (P = 0.95) in the placebo group. A subgroup analysis of those patients with TPOAb greater than 1200 IU/ml revealed a mean 40% reduction in the

selenium-treated patients compared with a 10% increase in TPOAb in the placebo group. TgAb concentrations were lower in the placebo group at the beginning of the study and significantly further decreased ($P = 0.018$), but were unchanged in the selenium group. Nine patients in the selenium-treated group had completely normalized antibody concentrations, in contrast to two patients in the placebo group (by χ^2 test, $P = 0.01$). Ultrasound of the thyroid showed normalized echogenicity in these patients. The mean TSH, free T4, and free T3 levels were unchanged in both groups.

We conclude that selenium substitution may improve the inflammatory activity in patients with autoimmune thyroiditis, especially in those with high activity. Whether this effect is specific for autoimmune thyroiditis or may also be effective in other endocrine autoimmune diseases has yet to be investigated.

CHRONIC AUTOIMMUNE thyroiditis with euthyroidism or hypothyroidism is a common disease, affecting more than 10% of females and 2% of males. There are several explanations for the development of this disease. There is a genetic background, as patients with human leukocyte antigens DR3 and DR5 and polymorphism of the cytotoxic T lymphocyte A4 promoter are more susceptible to the development of autoimmune thyroiditis compared with the normal population. There also are environmental factors, such as iodide intake, immunotherapeutic agents, or viral infections, that may initiate the disease (1).

In areas with combined endemic selenium and iodine deficiency, the supplementation of iodide alone leads to myxedematous cretinism (2, 3), which is defined by not only fetal hypothyroidism, but persistent hypothyroidism from early life. The thyroid of these patients is small and firm, suggesting fibrotic degeneration initiated by thyroid cell damage (4). The cause of this cell damage has been further investigated in animal studies. In severe selenium deficiency, the activity of the selenoenzyme glutathione peroxidase (GPx) is decreased, and therefore peroxide cleavage within the thyroid cells is diminished. Severe nutritional selenium deficiency therefore leads to an increased rate of thyroid cell necrosis and invasion of macrophages (5, 6). Whether this also may induce a higher incidence of autoimmune thyroiditis is unknown. It may be assumed, however, that thyroid cell damage may initiate or maintain autoimmune thyroiditis, especially in patients susceptible to the development of autoimmune diseases (7).

Furthermore, selenium has an important impact on immune function (8, 9). Selenium deficiency is accompanied by loss of immune competence. Both cell-mediated immunity and B cell function can be impaired. This might be related to the fact that the selenium-dependent enzymes, GPx and thioredoxin reductase (TxR), have antioxidative effects; they decrease free radical formation and reduce hydrogen peroxide and lipid and phospholipid hydroperoxides (9). In selenium-sufficient environment, the hydroperoxide intermediates of the cyclooxygenase and lipoxygenase pathways are therefore reduced and lead to diminished production of proinflammatory PGs and leukotrienes (10). In addition, both GPx and TxR modulate the respiratory burst and reduce superoxide production (11, 12, 13).

The possible therapeutic effect of selenium has already been shown in a double blind, randomized trial in patients with rheumatoid arthritis, in whom the supplementation of 200 μg selenium for 3 months significantly reduced pain and joint involvement (14). Selenium supplementation of 500-1000 μg has also been shown to improve survival in patients with hemorrhagic pancreatitis (15) and severe sepsis (16), which may be due to the antiinflammatory effect of a higher selenium supply.

The three known deiodinases also are selenium-dependent enzymes (11, 17, 18, 19). Their activity, however, in contrast to GPx activity, is only decreased in extremely severe selenium deficiency. T4 plasma concentrations are then elevated, and selenium supplementation lowers T4 and increases T3 concentrations (20).

In Germany, there is mild iodine deficiency (21) as well as mild selenium deficiency, as in most European countries (22). As selenium deficiency may influence both the immune response as well as peroxidation of thyroid cell

components, it seems reasonable to investigate whether a selenium substitution may influence the natural course of chronic autoimmune thyroiditis (23). There is one small pilot study showing a significant decrease in both thyroid peroxidase antibodies (TPOAb) as well as TSH receptor antibody concentrations in patients with lymphocytic autoimmune thyroiditis (24). We therefore conducted a blinded, placebo-controlled study in patients with chronic autoimmune thyroiditis to show whether supplementation with 200 µg (2.53 µmol) sodium selenite has any effect on plasma TPOAb concentrations, free thyroid hormones, and the ultrasound pattern of the affected thyroid in patients with overt autoimmune thyroiditis.

Subjects and Methods

Patient selection and treatment

Caucasian patients with known autoimmune thyroiditis and elevated plasma TPOAb and/or Tg antibodies (TgAb) above 350 IU/ml were selected from our out-patient clinic and asked for their informed consent to participate in the study. Diagnoses had been made by elevated TPOAb, TgAb, and basal TSH levels as well as typical hypoechoogenicity of the thyroid in high resolution sonography (25). From 92 patients selected, 71 agreed to participate in the study. They were randomized into 2 groups according to their initial TPOAb concentrations, age, and supposed duration of the disease. All patients were receiving L-T4 replacement therapy in a dosage to maintain basal TSH within the normal range. Patients then received either 200 µg sodium selenite/d (verum), orally, or placebo for 90 d. The patients were asked to take the medication with water about 2 h before or after a meal. They were not given further treatment, such as over-the-counter vitamins or trace elements.

All patients were otherwise healthy, but 3 in the placebo group and 4 in the treated group suffered from vitiligo, and 3 in both groups had mild rheumatoid arthritis. Many of the patients (8 in the placebo group and 12 in the verum group) had a history of various allergies, such as hay fever, neurodermitis, nickel and mercury allergy, and asthma, but none of the patients was receiving corticoid or other antiinflammatory therapy.

The primary end point of the study was the change in TPOAb concentrations. Secondary end points were TgAb, TSH, and free thyroid hormone levels as well as ultrasound pattern of the thyroid and quality of life estimation.

Laboratory and technical investigations

Blood samples were drawn initially and at the end of the treatment. Plasma total TPOAb and TgAb concentrations were measured by a commercial enzyme luminescence assay (Byk-Sangtec, Dietzenbach, Germany). The specificity for autoimmune thyroiditis in these assays is greater than 90% when antibody concentrations are above 350 IU/ml. Free T4 and T3 concentrations and TSH were measured by an enzyme immunometric assay (Byk-Sangtec). Plasma selenium was determined by atomic absorption spectrometry (26).

High resolution ultrasound (7.5 MHz; SONOLINE Elegra, Siemens, Erlangen, Germany) of the thyroid gland was performed, and echogenicity as well as perfusion by Doppler sonography were documented and compared at the beginning and end of the study by an independent experienced investigator (25).

The subjective well-being was evaluated using the standardized SF 12 protocol before and after the study. The SF 12 protocol is a 12 item short-form to survey health status in medical outcome studies.

Statistics

The relative changes in antibody concentrations as well as thyroid hormone concentrations in both groups were compared using Wilcoxon's matched pairs, signed-ranks test. In addition, the differences in antibody concentrations at the beginning and end of the study were determined by t test for paired samples. The P values were corrected for the numbers of tests performed. Subgroup analyses were conducted using 2 testing.

Results

A total of 71 patients, all females, were enrolled in the study, one was omitted because of pregnancy during the study period. Thirty-four received placebo; the other 36 received a liquid solution of 200 µg (2.53 µmol) sodium selenite/d. The mean age in both groups was identical (verum, 41.6 ± 12.1 yr; placebo, 43.0 ± 12.1 yr).

At study entry the mean TPOAb concentrations were identical in both groups (verum, 904 ± 205 IU/ml; placebo, 1090 ± 277 IU/ml), whereas the TgAb concentrations were significantly lower in the placebo group (verum, 1507 ± 390 IU/ml; placebo, 1089 ± 255 IU/ml; $P = 0.05$). TSH, free T4, and free T3 were identical in both groups. All were euthyroid under L-T4 treatment; the mean basal TSH levels were 1.2 ± 1.5 µU/ml (verum) and 1.4 ± 2.0 µU/ml (placebo). The ultrasound pattern in all patients revealed the typical hypoechoic thyroid tissue. None of the patients had thyroid nodules.

TPOAb concentrations significantly decreased in the verum group to 63.6% compared with that at study entry (100%) or in absolute values from a mean of 904 ± 205 to 575 ± 146 IU/ml ($P = 0.013$, by Wilcoxon's matched pairs test; $P = 0.016$, by paired t test). In contrast, in the placebo group using both statistical tests there was no change ($P = 0.95$ and $P = 0.32$, respectively); the TPOAb concentrations were 959 ± 267 IU/ml at the end of the study and 1090 ± 277 IU/ml at study entry (Fig. 1). There was no significant correlation between the plasma selenium concentrations and TPOAb before and after treatment.

A subgroup analysis of patients with TPOAb greater than 1200 IU/ml (verum, $n = 12$; placebo, $n = 8$) revealed a decrease in antibody concentrations in this group to 60% in the selenium group vs. an increase of 10% in the placebo group.

The mean TgAb concentrations at study entry were not identical in the two groups, because patients were randomized primarily according to the TPOAb concentrations. The TgAb concentration in the selenium-treated patients decreased to 91.2% compared with that at study entry (100%) or in absolute values from a mean of 1507 ± 390 to 1375 ± 484 IU/ml, which is not significant ($P = 0.33$). In the placebo group TgAb concentrations dropped from 1089 ± 225 to 742 ± 161 IU/ml ($P = 0.014$, by Wilcoxon's paired test; $P = 0.015$, by t test for paired samples; Table 1).

A decrease in both antibody concentrations below 50 IU/ml was detected in nine patients in the selenium-treated group vs. two patients in the placebo group (by 2 test, $P = 0.015$).

Free T4 and T3 as well as TSH values were unchanged in both groups, and all were within the normal range.

Plasma selenium values were identical in both groups at study entry (verum, 0.87 ± 0.15 µmol/liter; placebo, 0.91 ± 0.15 µmol/liter), increased significantly to 1.09 ± 0.12 µmol/liter in the verum group ($P = 0.001$), and were unchanged in the placebo group (0.92 ± 0.23 µmol/liter) at the end of the study (Fig. 2).

Improvement of ultrasound echogenicity was observed in nine patients in the selenium-treated group vs. two patients in the placebo group. These were identical to those patients with a decrease in antibody concentrations below 50 IU/ml, except for one patient in the placebo group.

Evaluation of subjective well-being revealed an improvement in 25 patients in the selenium-treated group compared with 6 in the placebo group, no change in 10 patients in the verum group vs. 26 in the placebo group, and worsening in 1 patient in the verum group vs. 4 in the placebo group (Fig. 3).

Discussion

In this randomized, prospective, blinded study we could demonstrate that in patients with autoimmune thyroiditis under selenium substitution with 200 µg (2.53 µmol)/d for 3 months, thyroid-specific TPOAb concentrations

significantly decreased from 100% to 63.6%. Even more important, in 9 of 36 patients, complete normalization of TPOAb concentrations as well as thyroid ultrasound echogenicity could be achieved with selenium supplementation compared with only 2 of 34 age- and TPOAb-matched controls.

In contrast to TPOAb concentrations, TgAb concentrations slightly decreased in the selenium-treated group, but significantly decreased in the placebo group. This might be due to the fact that the TgAb concentrations were already significantly lower in the placebo group at study entry compared with those in the verum group. The change in TgAb has been selected as a secondary end point of the study, because TgAb are less specific for autoimmune thyroiditis. However, plasma TPOAb concentrations are specific for autoimmune thyroiditis, thought to reflect intrathyroidal inflammation, and assumed to be cytotoxic in the presence of complement (1). Tg, in contrast to thyroid peroxidase, is a component normally secreted into the circulation and therefore is not necessarily an antigen only expressed during a thyroid-specific autoimmune response. Therefore, TgAb concentrations are less important for pathogenesis as well as diagnosis of autoimmune thyroiditis.

Selenium-dependent enzymes have diverse effects not only within the thyroid (19, 27), but also on the immune system (11, 23, 28, 29). It has been shown that during severe selenium deficiency, the lack of GPx activity may contribute to oxidative damage of the thyroid cell and initiation of thyroid damage and fibrosis (4). Selenium substitution in a rat model could prevent this oxidative damage (6). It might be supposed that even in mild selenium deficiency, this mechanism is an important environmental factor initiating or maintaining autoimmune thyroiditis in people genetically susceptible for the development of organ specific autoimmunity.

The immune modulatory effects of selenium-dependent enzymes such as GPx and TxR are involved in the organ-specific immune response (8, 10). This was demonstrated in selenium-deficient mice, where tissue damage of the lung was significantly increased after virus infection compared with selenium-adequate mice (30). The same is true for myocarditis in mice infected with coxsackie virus (31). The increased oxidative stress in all inflamed tissue leads to increased nuclear factor- κ B expression, particularly in selenium deficiency, leading to enhanced chemokine mRNA expression (32, 33). In addition, it has been shown that in selenium-deficient mice, CD8⁺ lymphocytes are significantly lower than in selenium-adequate mice, and the cytokine pattern is skewed toward a T helper cell 2-like pattern, which leads to increased inflammation in lung tissue after virus infection (30). Selenium-dependent enzymes are both antioxidative and antiinflammatory (11, 13, 22). This is because GPx can reduce hydrogen peroxides and lipid and phospholipid hydroperoxides, thereby lowering the propagation of free radicals and reactive oxygen species. Lower hydroperoxide tissue concentrations diminish the production of inflammatory PGs and leukotrienes. The respiratory burst is also dampened by selenium-dependent enzymes as well as superoxide production (10).

Although tissue damage after viral infection is not comparable to organ-specific autoimmunity, these investigations clearly demonstrates the striking effects of different nutritional selenium supply on the immune response (29). These mechanisms may also contribute to reduced inflammatory activity in the organ-specific autoimmune response (23, 34) and may explain the improvement of autoimmune thyroiditis in our study. In a nonblinded pilot study, significant decreases in TPOAb and thyroid binding inhibitory Igs, but not TgAb, concentrations were described in patients with Hashimoto's thyroiditis and Graves' disease (24), in accordance with our findings in patients with autoimmune thyroiditis.

The beneficial effect of a selenium supplementation of 200 μ g (2.53 μ mol)/d has also been shown clinically in double blind studies in rheumatoid arthritis (14) and asthma (34). In Crohn's disease, plasma selenium and GPx activities are inversely correlated to the activity of the disease (35).

We did not find any alterations in thyroid function after selenium supplementation. This might be due to the fact that the selenium deficiency was only moderate, and deiodinase activity decreases only in severe selenium deficiency (11). In a previous study in a small cohort of patients with reduced thyroid iodine organification after subacute

thyroiditis or postpartum thyroiditis (36), supplementation with 100 µg (1.26 µmol) selenium had no effect on thyroid hormone synthesis. The thyroid is one of the organs with the highest selenium concentration (37), but during mild selenium deficiency deiodinase activities are unaltered, in contrast to GPx activities. Therefore, in tissue samples from patients with autoimmune thyroiditis and nontoxic goiter, there was no difference in selenium tissue concentration in selenium-sufficient areas (38). The selenium deficiency in our patients was mild (0.89 µmol/liter), but it is known that in individuals with such low plasma selenium concentrations GPx activity is impaired. The mean plasma selenium concentration necessary for optimal GPx activities is 1.20 µmol/liter (range, 1.12–1.44 µmol/liter) (39). This might explain the antiinflammatory activity of selenium without its affecting thyroid hormone levels.

We also determined quality of life in our study population. The change in antibody concentrations or inflammatory activity within the thyroid of course has no impact on quality of life, but there are studies showing that low selenium intake is associated with a significant greater incidence of negative mood states and depression (40, 41). Patients receiving selenium supplementation reported significantly better well-being in our trial compared with the placebo group, which supports these earlier findings (42). The cause is unknown, but there are indications that selenium is important for brain function. The turnover rate of some neurotransmitters is altered in selenium deficiency (43), and low plasma selenium concentrations are associated with senility and cognitive decline (44).

The conclusion of our study is that even in mild selenium deficiency the supplementation of this important trace element has a significant impact on inflammatory activity in thyroid-specific autoimmune disease. It would be of interest to determine whether early treatment with selenium in patients with newly developed autoimmune thyroiditis and, even more importantly, in those with Graves' disease may delay or even prevent the natural course of these diseases. It also is important to further evaluate whether selenium supplementation is effective in modulation of other organ-specific autoimmune diseases such as type I diabetes. The results of our study should encourage the initiation of further clinical trials to elucidate the beneficial effects of sufficient selenium supplementation.

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Footnotes

Abbreviations: GPx, Glutathione peroxidase; TgAb, Tg antibodies; TPOAb, thyroid peroxidase antibodies; TxR, thioredoxin reductase.

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