

ABSTRACTS

Zeaxanthin

Are lutein and zeaxanthin conditionally essential nutrients for eye health?

The carotenoids lutein and zeaxanthin are found in the macula in high concentrations and may play a role in the pathogenesis of age-related macular degeneration (ARMD). Lutein and zeaxanthin may protect the macula and photoreceptor outer segments throughout the retina from oxidative stress and play a role in an antioxidant cascade that safely disarms the energy of reactive oxygen species. Although lutein and zeaxanthin are not essential nutrients, studies are beginning to suggest that they fit the criteria for conditionally essential nutrients. Low plasma lutein and zeaxanthin concentrations or dietary intake are associated with low macular pigment density and increased risk of ARMD. Dietary deprivation of lutein and zeaxanthin in primates causes pathological changes in the macula. Should controlled clinical trials show lutein and/or zeaxanthin supplementation protects against the development or progression of ARMD and other eye diseases, then lutein and zeaxanthin could be considered as conditionally essential nutrients for humans.

Med Hypotheses. 2003 Oct;61 (4):465-72

Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye.

The macular region of the primate retina is yellow in color due to the presence of the macular pigment, composed of two dietary xanthophylls, lutein and zeaxanthin, and another xanthophyll, meso-zeaxanthin. The latter is presumably formed from either lutein or zeaxanthin in the retina. By absorbing blue-light, the macular pigment protects the underlying photoreceptor cell layer from light damage, possibly initiated by the formation of reactive oxygen species during a photosensitized reaction. There is ample epidemiological evidence that increased macular pigment is correlated with reduced incidence of age-related macular degeneration, an irreversible process that is the major cause of blindness in the elderly. The macular pigment can be increased in primates by either increasing the intake of foods that are rich in lutein and zeaxanthin, such as dark-green leafy vegetables, or by supplementation with lutein or zeaxanthin. Although increasing the intake of lutein or zeaxanthin might prove to be protective against the development of age-related macular degeneration, a causative relationship has yet to be experimentally demonstrated.

Annu Rev Nutr. 2003;23:171-201. Epub 2003 Feb 27

Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins.

Epidemiologic data indicate that individuals with low plasma concentrations of carotenoids and antioxidant vitamins and those who smoke cigarettes are at increased risk for age-related macular degeneration (AMD). Laboratory data show that carotenoids and antioxidant vitamins help to protect the retina from oxidative damage initiated in part by absorption of light. Primate retinas accumulate two carotenoids, lutein and zeaxanthin, as the macular pigment, which is most dense at the center of the fovea and declines rapidly in more peripheral regions.

The retina also distributes alpha-tocopherol (vitamin E) in a nonuniform spatial pattern. The region of monkey retinas where carotenoids and vitamin E are both low corresponds with a locus where early signs of AMD often appear in humans. The combination of evidence suggests that carotenoids and antioxidant vitamins may help to retard some of the destructive processes in the retina and the retinal pigment epithelium that lead to age-related degeneration of the macula.

Am J Clin Nutr. 1995 Dec;62(6 Suppl):1448S-1461S

C-reactive protein concentration and concentrations of blood vitamins, carotenoids, and selenium among United States adults.

OBJECTIVE: To examine the relationships between circulating concentrations of C-reactive protein and concentrations of retinol, retinyl esters, vitamin C, vitamin E, carotenoids, and selenium. **DESIGN:** Cross-sectional study using National Health and Nutrition Examination Survey III (1988-1994) data. **SETTING:** United States population. **SUBJECTS:** Up to 14,519 US noninstitutionalized civilian men and women aged ≥ 20 y. **RESULTS:** C-reactive protein concentration (dichotomized at the sex-specific 85th percentile) was inversely and significantly associated with concentrations of retinol, retinyl esters, vitamin C, alpha-carotene, beta-carotene, cryptoxanthin, lutein/zeaxanthin, lycopene, and selenium after adjustment for age, sex, race or ethnicity, education, cotinine concentration, body mass index, leisure-time physical activity, and aspirin use. **CONCLUSIONS:** These results suggest that the inflammatory process, through the production of reactive oxygen species, may deplete stores of antioxidants. Whether increased consumption of foods rich in antioxidants or supplementation with antioxidants can provide

health benefits to people characterized by elevated C-reactive protein concentrations may be worthy of further study.

Eur J Clin Nutr. 2003 Sep;57 (9):1157-63

Nutritional and clinical relevance of lutein in human health.

Lutein is one of the most widely found carotenoids distributed in fruits and vegetables frequently consumed. Its presence in human tissues is entirely of dietary origin. Distribution of lutein among tissues is similar to other carotenoids but, along with zeaxanthin, they are found selectively at the centre of the retina, being usually referred to as macular pigments. Lutein has no provitamin A activity in man but it displays biological activities that have attracted great attention in relation to human health. Epidemiological studies have shown inconsistent associations between high intake or serum levels of lutein and lower risk for developing cardiovascular disease, several types of cancer, cataracts and age-related maculopathy. Also, lutein supplementation has provided both null and positive results on different biomarkers of oxidative stress although it is effective in increasing macular pigment concentration and in improving visual function in some, but not all, subjects with different eye pathologies. Overall, data suggest that whereas serum levels of lutein have, at present, no predictive, diagnostic or prognostic value in clinical practice, its determination may be very helpful in assessing compliance and efficacy of intervention as well as potential toxicity. In addition, available evidence suggests that a serum lutein concentration between 0.6 and 1.05 micromol/l seems to be a safe, dietary achievable and desirable target potentially associated with beneficial impact on visual function and, possibly, on the development of other chronic diseases. The use of lutein as a biomarker of exposure in clinical practice may provide some rationale for assessing its relationship with human health as well as its potential use within the context of evidence-based medicine.

Br J Nutr. 2003 Sep;90(3):487-502

Dietary lutein/zeaxanthin decreases ultraviolet B-induced epidermal hyperproliferation and acute inflammation in hairless mice.

Lutein and zeaxanthin are carotenoids found in green leafy vegetables with interesting antioxidant properties. They are present in high concentrations in the fovea centralis of the human retina and their role in the prevention of age-related macula degeneration has been reported. We have investigated the effect of orally administered lutein and zeaxanthin in the cutaneous response to ultraviolet B irradiation. Female hairless SKh-1 mice receiving 0.4% and 0.04% lutein plus zeaxanthin-enriched diet for 2 weeks were exposed to single doses of ultraviolet B radiation. Skin biopsies were taken at 24 and 48 hours after irradiation and analyzed for the presence of apoptotic cells, proliferating cells, and expression of proliferating cell nuclear antigen. Our results show a clear ultraviolet-induced dose-dependent inflammatory response. Orally administered 0.4% lutein and zeaxanthin decreased significantly the edematous cutaneous response ($p < 0.01$) as determined by the reduction of the UVB-induced increase of ear bifold thickening. Additionally, dietary carotenoids were efficient in reducing the ultraviolet B-induced increases in the percentage of proliferating cell nuclear antigen ($p < 0.05$), bromodeoxyuridine ($p < 0.05$), and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling-positive cells ($p < 0.01$). These data demonstrate that oral supplementation of lutein and zeaxanthin diminishes the effects of ultraviolet B irradiation by reducing acute inflammatory responses and ultraviolet-induced hyperproliferative rebound.

J Invest Dermatol. 2003 Aug;121 (2):399-405

Effect of dietary zeaxanthin on tissue distribution of zeaxanthin and lutein in quail.

PURPOSE: The xanthophyll carotenoids (lutein and zeaxanthin) are hypothesized to delay progression of age-related macular degeneration. The quail has a cone-dominant retina that accumulates carotenoids. The purpose of these experiments was to characterize the carotenoid composition of retina, serum, liver, and fat in quail and to determine whether dietary enrichment with zeaxanthin alters zeaxanthin or lutein concentrations in these tissues. **METHODS:** Quail were fed for 6 months with a commercial turkey diet (T group; $n = 8$), carotenoid-deficient diet (C- group; $n = 8$), or a carotenoid-deficient diet supplemented with 35 mg 3R, 3'R-zeaxanthin per kilogram of food, (Z+ group; $n = 8$). Zeaxanthin was derived from *Sphingobacterium multivorum* (basonym *Flavobacterium*). Carotenoids in serum, retina, liver, and fat were analyzed by HPLC. **RESULTS:** As in the primate fovea, the retina accumulated zeaxanthin, lutein, and cryptoxanthin, and preferentially absorbed zeaxanthin ($P < 0.005$). In contrast, lutein was preferentially absorbed by liver ($P < 0.01$) and fat ($P < 0.0001$). In supplemented females, zeaxanthin increased approximately 4-fold in retina, and 74-, 63- and 22-fold in serum, liver, and fat, respectively. In males, zeaxanthin was elevated approximately 3-fold in retina, and 42-, 17-, and 12-fold in serum, liver, and fat, respectively. Birds fed the Z+ diet absorbed a higher fraction of dietary lutein into serum, but lutein was reduced in the retina ($P < 0.05$). **CONCLUSIONS:** Xanthophyll profiles in quail mimic those in primates. Dietary supplements of zeaxanthin effectively increased zeaxanthin concentrations in serum, retina, liver, and fat. The robust response to zeaxanthin supplementation identifies the quail as an animal model for exploration of factors regulating delivery of dietary carotenoids to the retina.

Invest Ophthalmol Vis Sci. 2002 Apr;43(4):1210-21

ABSTRACTS

Aging Eye

Blood and lens lipid peroxidation and antioxidant status in normal individuals, senile and diabetic cataractous patients.

PURPOSE: Oxidative mechanisms are believed to play an important role in the pathogenesis of cataract, the most important cause of visual impairment at advanced age. To determine the body's antioxidant status as well as its lipid peroxidation levels, both blood and lens parameters were evaluated. **METHODS:** This study was performed on the blood samples and lenses obtained from 46 patients diagnosed as having cataract and 20 control subjects. The control group was composed of 10 women and 10 men who do not smoke. Control subjects without any lens opacity or vacuoles when observed with a slit lamp were recruited on the same exclusion criteria as far as disease and treatment were concerned. No antioxidant medicines were used. They were all healthy individuals without any systemic diseases. Superoxide dismutase (SOD), glucose-6-phosphate dehydrogenase (G6PD), glutathione reductase (GSSG-Red) activities in red blood cell (RBC) lysates as well as whole blood glutathione (GSH) and plasma thiobarbituric acid reactive substances (TBARS), the indicator of lipid peroxidation concentrations, were determined quantitatively both in the blood samples and the lenses of the patients with senile and diabetic cataracts. **RESULTS:** Whole blood GSH values, and erythrocyte SOD activities were significantly lower in the cataractous patients than those in the control group. The values in the diabetic cataractous group were also less than those in the senile cataractous group. Significantly decreased erythrocyte GSSG-Red and G6PD activities were detected in the diabetic cataractous group. Plasma TBARS values were higher both in the senile and diabetic groups when compared to those in the control group. Significantly decreased values were observed for GSSG-Red activities and TBARS values in the lenses of the senile cataractous patients in comparison with those in the diabetic cataractous patients. The lens GSH values were found to be higher in the senile cataractous group than the values obtained in the diabetic cataractous group. **CONCLUSIONS:** A strong correlation was found between lens GSH and lens TBARS concentrations in the diabetic group. This emphasized the vital role of GSH as an antioxidant in the lens over the other antioxidant parameters, e.g., enzymes, and the oxidative stress is at the highest level in lens.

Curr Eye Res. 2002 Jul;25(1):9-16

Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities.

BACKGROUND: Proper nutrition appears to protect against cataracts. Few studies have related nutrition to the odds of developing cortical or posterior subcapsular (PSC) cataracts. **OBJECTIVE:** We assessed the relation between usual nutrient intakes and age-related cortical and PSC lens opacities. **DESIGN:** We studied 492 nondiabetic women aged 53-73 years from the Nurses' Health Study cohort who were without previously diagnosed cataracts. Usual nutrient intake was calculated as the average intake from 5 food-frequency questionnaires collected over a 13-15-year period before the eye examination. Duration of vitamin supplement use was determined from 7 questionnaires collected during this same period. We defined cortical opacities as grade ≥ 0.5 and subcapsular opacities as grade ≥ 0.3 of the Lens Opacities Classification System III. **RESULTS:** Some lenses had more than one opacity. No nutrient measure was related to prevalence of opacities in the full sample, but significant interactions were seen between age and vitamin C intake ($P = 0.02$) for odds of cortical opacities and between smoking status and folate ($P = 0.02$), alpha-carotene ($P = 0.02$), beta-carotene ($P = 0.005$), and total carotenoids ($P = 0.02$) for odds of PSC opacities. For women aged <60 years old, a vitamin C intake ≥ 362 mg/d was associated with a 57% lower odds ratio (0.43; 95% CI: 0.2, 0.93) of developing a cortical cataract than was an intake <140 mg/d, and use of vitamin C supplements for ≥ 10 y was associated with a 60% lower odds ratio (0.40; 0.18, 0.87) than was no vitamin C supplement use. Prevalence of PSC opacities was related to total carotenoid intake in women who never smoked ($P = 0.02$). **CONCLUSIONS:** Our results support a role for vitamin C in diminishing the risk of cortical cataracts in women aged <60 years old and for carotenoids in diminishing the risk of PSC cataracts in women who have never smoked.

Am J Clin Nutr. 2002 Mar;75 (3):540-9

Vitamin C is associated with reduced risk of cataract in a Mediterranean population.

Cataract is an important visual problem of older people and a substantial health care cost in many countries. Most studies investigating risk factors for cataract have been conducted in the United States, and there is less information on the possible role of dietary factors in European populations. We conducted a case-control study to investigate the association of antioxidant vitamins (vitamin C, vitamin E, vitamin A, beta-carotene, alpha-carotene, beta-cryptoxanthin, lycopene, zeaxanthin and lutein) and minerals (zinc and selenium) and risk of cataract in a Mediterranean population. Cases with cataract (343) and 334 age/sex frequency-matched controls aged 55 to 74 years old were selected from an ophthalmic outreach clinic in Valencia, Spain. Participants were interviewed about their diet using a Food Frequency Questionnaire, and other information on potential confounders, such as smoking, alcohol, and education. Blood samples were

analyzed by a colorimetric method for vitamin C and by reversed-phase HPLC for other blood antioxidants. Blood levels of vitamin C above 49 micromol/L were associated with a 64% reduced odds for cataract ($P < 0.0001$). Dietary intake of vitamins C, E and selenium were marginally associated with decreased odds ($P = 0.09$, $P = 0.09$, $P = 0.07$, respectively), whereas moderately high levels of blood lycopene (>0.30 micromol/L) were associated with a 46% increased odds of cataract ($P = 0.04$). Our results strengthen the evidence for a protective role for vitamin C on the aging lens as this effect was seen in a population characterized by high vitamin C intakes.

J Nutr. 2002 Jun;132(6):1299-306

ABSTRACTS

Blood Testing

Serum interleukin-6 and bone metabolism in patients with thyroid function disorders.

To determine the possible involvement of interleukin-6 (IL-6) in the bone loss of hyperthyroidism, relationships between thyroid status, biochemical and densitometric parameters of bone metabolism, and IL-6 were studied in female subjects. Patients with hyperthyroidism caused by either toxic nodular goiter or Graves' disease had significantly higher serum IL-6 concentrations than normal controls. Within the control group, serum IL-6 was higher in postmenopausal than in premenopausal women, but this influence of menopausal status was not seen in the hyperthyroid patients. The production of IL-6 by blood mononuclear cells was higher in cells from the hyperthyroid women. Bone turnover was increased in the hyperthyroid patients based on serum osteocalcin and urinary deoxypyridinoline excretion, and the hyperthyroid group also had reduced radius bone mineral content (BMC). A subgroup of hyperthyroid patients who had the lowest BMC (values more than 1 SD below normal age-matched controls) also had serum IL-6 concentrations significantly greater than those of hyperthyroid patients showing less reduction of BMC. The correlations observed in this study support the possibility that IL-6 plays a role in mediating the bone loss that results from excess thyroid hormone.

J Clin Endocrinol Metab. 1997 Jan;82(1):78-81

Serum interleukin 6 is a major predictor of bone loss in women specific to the first decade past menopause.

The role of serum interleukin 6 (IL-6) as a predictor of bone loss was examined in a population-based, longitudinal study of 137 postmenopausal German women, 52-80 years old at baseline. Serum IL-6 and other biochemical parameters were measured in baseline blood or urine specimens. Repeat standardized measures of bone mineral density (BMD) at the femur (total hip) and the lumbar spine (L2-L4) were taken by dual x-ray absorptiometry an average of 3.3 yr apart. Medical history and anthropometric measures were obtained from standardized interview and examination. Crude and age-adjusted mean serum IL-6 levels were significantly lower in postmenopausal women with than without hormone replacement therapy at baseline. Among nonusers of hormone replacement therapy, serum IL-6 concentrations were highly predictive of femoral bone loss, independently of potential confounders and plasma sex hormones. Statistical interaction between serum IL-6 and menopausal age or menopausal age group (>10 vs. < or =10 years) indicated that the effect of IL-6 on bone loss weakened with increasing distance from menopause and was no longer significant in women more than 10 years after menopause. Among women up to 10 years past menopause (n = 39), serum IL-6 was the single most important predictor of femoral bone loss, accounting for up to 34% of the total variability of change in BMD. The unadjusted linear model predicted an annual 1.34% (95% confidence interval, 0.67-2.01) decrease in total hip BMD per log unit increase in serum IL-6. A similar, although nonsignificant, effect of serum IL-6 on vertebral bone loss was restricted to women within the first 6 years after menopause (n = 18). These epidemiological data show that serum IL-6 is a predictor of postmenopausal bone loss, and that the effect appears to be most relevant through the first postmenopausal decade. Whether these findings reflect pathogenetic differences between early and postmenopausal bone loss, and whether serum IL-6 also predicts fracture risk need further elucidation.

J Clin Endocrinol Metab. 2001 May;86(5):2032-42

Monitoring estrogen replacement therapy and identifying rapid bone losers with an immunoassay for deoxypyridinoline.

We have assessed urinary deoxypyridinoline (Dpd) levels by immunoassay in women who participated in a double-masked, placebo-controlled trial of the bone loss prevention effects of estrogen replacement therapy (ERT). Ninety-one women who had undergone recent surgical menopause were randomized to receive either placebo or 0.025, 0.05 or 0.1 mg/day transdermal 17 beta-estradiol for 2 years. Mean Dpd levels in the postmenopausal women were significantly elevated ($p < 0.0001$) above mean Dpd levels in a reference population of healthy, premenopausal women. Subjects in the placebo group lost 6.4% of lumbar spine bone mineral density (BMD) and 4.9% of mid-radius bone mineral content (BMC) over 2 years. Dpd levels at baseline were inversely correlated with BMD and BMC changes in the placebo group. The placebo group and subjects receiving 0.025 mg/day 17 beta-estradiol who had Dpd levels increased above the reference interval cut-off (mean + 2 standard deviations, 7.5 nmol/mmol) lost 2 times more bone mass than did those with Dpd levels below it. Dpd levels decreased significantly ($p < 0.01$) from baseline at 6 months following initiation of treatment with 0.05 or 0.1 mg/day 17 beta-estradiol, changes that correlated with increased lumbar spine BMD and with changes in mid-radius BMC. At 12 months, Dpd levels were lower than baseline and placebo in all three treatment groups. These data suggest utility of this Dpd immunoassay in assessing changes in bone resorption induced by surgical menopause and ERT.

Osteoporos Int. 1998;8(2):159-64

Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study.

Increased bone turnover has been suggested as a potential risk factor for osteoporotic fractures. We investigated this hypothesis in a prospective cohort study performed on 7,598 healthy women more than 75 years of age. One hundred and twenty-six women (mean years 82.5) who sustained a hip fracture during a mean 22-month follow-up were age-matched with three controls who did not fracture. Baseline samples were collected prior to fracture for the measurement of two markers of bone formation and three urinary markers of bone resorption: type I collagen cross-linked N- (NTX) or C-telopeptide (CTX) and free deoxypyridinoline (free D-Pyr). Elderly women had increased bone formation and resorption compared with healthy premenopausal women. Urinary excretion of CTX and free D-Pyr, but not other markers, was higher in patients with hip fracture than in age-matched controls ($p = 0.02$ and 0.005 , respectively). CTX and free D-Pyr excretion above the upper limit of the premenopausal range was associated with an increased hip fracture risk with an odds ratio (95% confidence interval) of 2.2 (1.3-3.6) and 1.9 (1.1-3.2), respectively, while markers of formation were not. Increased bone resorption predicted hip fracture independently of bone mass, i.e., after adjustment for femoral neck bone mineral density (BMD) and independently of mobility status assessed by the gait speed. Women with both a femoral BMD value of 2.5 SD or more below the mean of young adults and either high CTX or high free D-Pyr levels were at greater risk of hip fracture, with an odds ratio of 4.8 and 4.1, respectively, than those with only low BMD or high bone resorption. Elderly women are characterized by increased bone turnover, and some markers of bone resorption predict the subsequent risk of hip fracture independently of hip BMD. Combining the measurement of BMD and bone resorption may be useful to improve the assessment of the risk of hip fracture in elderly women.

J Bone Miner Res. 1996 Oct;11 (10):1531-8

High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism?

OBJECTIVE: The association between established hypothyroidism and high cholesterol levels is well known. The aim of the present study was to investigate the effect of thyroxine (T4) administration on cholesterol levels in hypercholesterolemic subjects with TSH levels within the normal range ('high-normal' TSH compared with 'low-normal' TSH). **DESIGN AND METHODS:** We determined TSH levels in 110 consecutive patients referred for hypercholesterolemia (serum cholesterol >7.5 mmol/l). Those with 'high-normal' TSH (2.0-4.0 microU/ml) as well as those with 'low-normal' TSH (0.40-1.99 microU/ml) were randomly assigned to receive either 25 or 50 microg T4 daily for two months. Thus, groups A and B (low-normal TSH) received 25 and 50 microg T4 respectively and groups C and D (high-normal TSH) received 25 and 50 microg T4 respectively. Serum T4, tri-iodothyronine (T3), TSH, free thyroxine index, resin T3 uptake and thyroid autoantibodies (ThAab) as well as total cholesterol, high and low density lipoprotein cholesterol (HDL, LDL), and triglycerides were determined before and at the end of the two-month treatment period. **RESULTS:** TSH levels were reduced in all groups. The most striking effect was observed in group D (TSH levels before: 2.77 ± 0.55 , after: 1.41 ± 0.85 microU/ml, $P < 0.01$). Subjects in groups C and D had a higher probability of having positive ThAabs. A significant reduction in total cholesterol ($P < 0.01$) and LDL ($P < 0.01$) was observed after treatment only in group D. In those subjects in group D who were ThAab negative, there was no significant effect of thyroxine on cholesterol levels. **CONCLUSIONS:** Subjects with high-normal TSH levels combined with ThAabs may, in fact, have subclinical hypothyroidism presenting with elevated cholesterol levels. It is possible that these patients might benefit from thyroxine administration.

Eur J Endocrinol. 1998 Feb;138 (2):141-5

Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study.

BACKGROUND: Overt hypo-thyroidism has been found to be associated with cardiovascular disease. Whether subclinical hypothyroidism and thyroid autoimmunity are also risk factors for cardiovascular disease is controversial. **OBJECTIVE:** To investigate whether subclinical hypothyroidism and thyroid autoimmunity are associated with aortic atherosclerosis and myocardial infarction in postmenopausal women. **DESIGN:** Population-based cross-sectional study. **SETTING:** A district of Rotterdam, The Netherlands. **PARTICIPANTS:** Random sample of 1,149 women (mean age \pm SD, 69.0 ± 7.5 years) participating in the Rotterdam Study. **MEASUREMENTS:** Data on thyroid status, aortic atherosclerosis, and history of myocardial infarction were obtained at baseline. Subclinical hypothyroidism was defined as an elevated thyroid-stimulating hormone level (>4.0 mU/L) and a normal serum free thyroxine level (11 to 25 pmol/L [0.9 to 1.9 ng/dL]). In tests for antibodies to thyroid peroxidase, a serum level greater than 10 IU/mL was considered a positive result. **RESULTS:** Subclinical hypothyroidism was present in 10.8% of participants and was associated with a greater age-adjusted prevalence of aortic atherosclerosis (odds ratio, 1.7 [95% CI, 1.1 to 2.6]) and myocardial infarction (odds ratio, 2.3 [CI, 1.3 to 4.0]). Additional adjustment for body mass index, total and high-density lipoprotein cholesterol level, blood pressure, and smoking status, as well as exclusion of women who took beta-blockers, did not affect these estimates. Associations were slightly stronger in women who had subclinical hypothyroidism and antibodies to thyroid peroxidase (odds ratio for aortic atherosclerosis, 1.9 [CI, 1.1 to 3.6]; odds ratio for myocardial infarction, 3.1 [CI, 1.5 to 6.3]). No association was found between thyroid autoimmunity itself and cardiovascular disease. The population attributable risk percentage for subclinical hypothyroidism associated with myocardial infarction was within the range of that for known major risk factors for cardiovascular disease. **CONCLUSION:** Subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women.

Ann Intern Med. 2000 Feb 15;132 (4):270-8

American Thyroid Association guidelines for detection of thyroid dysfunction.

OBJECTIVE: To define the optimal approach to identify patients with thyroid dysfunction. **PARTICIPANTS:** The 8-member Standards of Care Committee of the American Thyroid Association prepared a draft, which was reviewed by the association's 780 members, 50 of whom responded with suggested revisions. **EVIDENCE:** Relevant published studies were identified through MEDLINE and the association membership's personal resources. **CONSENSUS PROCESS:** Consensus was reached at group meetings. The first draft was prepared by a single author (P.W.L.) after group discussion. Suggested revisions were incorporated after consideration by the committee. **CONCLUSIONS:** The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter. The indication for screening is particularly compelling in women, but it can also be justified in men as a relatively cost-effective measure in the context of the periodic health examination. Individuals with symptoms and signs potentially attributable to thyroid dysfunction and those with risk factors for its development may require more frequent serum thyrotropin testing.

Arch Intern Med. 2000 Jun 12;160(11):1573-5

Acetyl-L-carnitine administration increases insulin-like growth factor 1 levels in asymptomatic HIV-1-infected subjects: correlation with its suppressive effect on lymphocyte apoptosis and ceramide generation.

The aim of this study was to investigate the impact of long-term acetyl-L-carnitine administration on CD4 and CD8 absolute counts, apoptosis, and insulin-like growth factor 1 (IGF-1) serum levels in HIV-1-infected subjects. The generation of cell-associated ceramide and HIV-1 viremia were also investigated. Eleven asymptomatic, HIV-1-infected subjects were treated daily with acetyl-L-carnitine (3 g) for 5 months. Immunologic and virologic measures and safety were monitored at the start of the treatment and then on days 90 and 150. Altogether our findings suggest that acetyl-L-carnitine administration has a substantial impact on the main immunologic abnormality associated with HIV infection, the loss of CD4 cells, by reducing the rate of apoptotic lymphocyte death. The reduction of ceramide generation and the increase of the serum levels of IGF-1, a major survival factor able to protect cells from apoptosis by different stimuli and conditions, could represent two important mechanisms underlying the observed anti-apoptotic effects of acetyl-L-carnitine.

Clin Immunol. 1999 Jul;92 (1):103-10

Serum insulin-like growth factor 1: tumor marker or etiologic factor?

Levels of insulin-like growth factor 1 (IGF-1), a neuroprotective hormone, decrease in serum during aging, whereas amyloid-beta (Abeta), which is involved in the pathogenesis of Alzheimer's disease, accumulates in the brain. High brain Abeta levels are found at an early age in mutant mice with low circulating IGF-1, and Abeta burden can be reduced in aging rats by increasing serum IGF-1. This opposing relationship between serum IGF-1 and brain Abeta levels reflects the ability of IGF-1 to induce clearance of brain Abeta, probably by enhancing transport of Abeta carrier proteins such as albumin and transthyretin into the brain. This effect is antagonized by tumor necrosis factor-alpha, a pro-inflammatory cytokine putatively involved in dementia and aging. Because IGF-1 treatment of mice overexpressing mutant amyloid markedly reduces their brain Abeta burden, we consider that circulating IGF-1 is a physiological regulator of brain amyloid levels with therapeutic potential.

Nat Med. 2002 Dec;8(12):1390-7. Epub 2002 Nov 04

Endogenous hormones and carotid atherosclerosis in elderly men.

The aging process is characterized by a number of gradual changes in circulating hormone concentrations as well as a gradual increase in the degree of atherosclerosis. The authors studied whether serum hormone levels are related to atherosclerosis of the carotid artery in independently living, elderly men. In 1996, 403 men (aged 73-94 years) were randomly selected from the general population of Zoetermeer, the Netherlands. Carotid artery intima-media thickness was determined. Serum concentrations of testosterone; estrone; estradiol; dehydroepiandrosterone and dehydroepiandrosterone sulfate; insulin-like growth factor I (IGF-1) (total and free) and its binding proteins IGFBP-1, IGFBP-2, and IGFBP-3; and leptin were measured. After the authors adjusted for age, serum testosterone, estrone, and free IGF-1 levels were correlated with greater intima-media thickness. The strength of these relations was as powerful in subjects with as in those without prevalent cardiovascular disease. Serum estradiol; dehydroepiandrosterone sulfate; total IGF-1, IGFBP-1, IGFBP-2, and IGFBP-3; and leptin showed no association. These findings suggest that endogenous testosterone, estrone, and free IGF-1 levels may play a protective role in the development of atherosclerosis in aging men.

Am J Epidemiol. 2003 Jan 1;157(1):25-31

Ageing and longevity are related to growth hormone/insulin-like growth factor 1 secretion.

BACKGROUND: It is known that the growth process is related to an individual's lifespan, but the role of growth hormone (GH) secretion in human ageing remains unknown. **OBJECTIVE:** This study has focussed on the influence of GH on ageing parameters and on its relationship with human longevity. **METHODS:** To deal with the first issue, we compared ageing parameters of young (up to 39) and old (over 70) individuals having similar insulin-like growth factor-1 (IGF-1) blood levels. For the second one, the decline in IGF-1 levels was studied comparing its behaviour in the first half with that in the second half of adult life. The latter represents the period of life in which mortality progressively increases. Two hundred and five healthy individuals

were chosen as subjects, well distributed by gender and age (between 19 and 93 years). RESULTS: Old males with IGF-1 levels similar to young ones do not show the age-dependent decrease in serum testosterone and lean body mass, nor the increase in fat body mass. Other hormone-metabolic and nutritional parameters do not reveal any change compared with the results of all individuals. In females, the results do not allow to assume any IGF-1 influence. The behaviour of the linear regression in the second half of adult life of males, which becomes flat because old men having low IGF-1 blood levels die earlier, is consistent with these results. This effect, which is supported by predictive analysis, is not observed in females, i.e. the IGF-1 level declines in the second half of the women's adult life are only a little flatter than in the first half. Finally, extrapolating the regressions obtained in the first half of adulthood, the age at which the curve crosses the x-axis is 110 years for males and 132 for females. CONCLUSIONS: The presented study of IGF-1 levels suggests that the GH secretion in adulthood plays a determinant role not only for some regressive manifestations, but also for life potential.

Gerontology. 2002 Nov-Dec;48 (6):401-7

Viral mediated expression of insulin-like growth factor 1 blocks the aging-related loss of skeletal muscle function.

During the aging process, mammals lose up to a third of their skeletal muscle mass and strength. Although the mechanisms underlying this loss are not entirely understood, we attempted to moderate the loss by increasing the regenerative capacity of muscle. This involved the injection of a recombinant adeno-associated virus directing overexpression of insulin-like growth factor 1 (IGF-1) in differentiated muscle fibers. We demonstrate that the IGF-1 expression promotes an average increase of 15% in muscle mass and a 14% increase in strength in young adult mice, and remarkably, prevents aging-related muscle changes in old adult mice, resulting in a 27% increase in strength as compared with uninjected old muscles. Muscle mass and fiber type distributions were maintained at levels similar to those in young adults. We propose that these effects are primarily due to stimulation of muscle regeneration via the activation of satellite cells by IGF-1. This supports the hypothesis that the primary cause of aging-related impairment of muscle function is a cumulative failure to repair damage sustained during muscle utilization. Our results suggest that gene transfer of IGF-1 into muscle could form the basis of a human gene therapy for preventing the loss of muscle function associated with aging and may be of benefit in diseases where the rate of damage to skeletal muscle is accelerated.

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HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study.

OBJECTIVE: To evaluate whether homeostasis model assessment estimated insulin resistance (HOMA-IR) is an independent predictor of cardiovascular disease (CVD) in type 2 diabetes. RESEARCH DESIGN AND METHODS: Conventional CVD risk factors (sex, age, smoking, plasma lipids, blood pressure, and metabolic control) and insulin resistance (estimated by HOMA) were evaluated at baseline in 1,326 patients with type 2 diabetes examined within the Verona Diabetes Complications Study. At baseline and after a mean follow-up of 4.5 years, CVD was assessed by medical history, physical examination, electrocardiography, and echo-Doppler of carotid and lower limb arteries. Death certificates and medical records of subjects who died during the follow-up were carefully scrutinized to identify cardiovascular deaths. In statistical analyses, CVD was an aggregate end point including both fatal and nonfatal coronary, cerebrovascular, and peripheral vascular disease as well as ischemic electrocardiographic abnormalities and vascular lesions identified by echo-Doppler. RESULTS: At baseline, 441 subjects were coded positive for CVD (prevalent cases). Incident cases numbered 126. Multiple logistic regression analyses showed that, along with sex, age, smoking, HDL/total cholesterol ratio, and hypertension, HOMA-IR was an independent predictor of both prevalent and incident CVD. A one-unit increase in (log)HOMA-IR value was associated with an odds ratio for prevalent CVD at baseline of 1.31 (95% CI 1.10-1.56, $P = 0.002$) and for incident CVD during follow-up of 1.56 (95% CI 1.14-2.12, $P < 0.001$). CONCLUSIONS: HOMA-IR is an independent predictor of CVD in type 2 diabetes. The improvement of insulin resistance might have beneficial effects not only on glucose control but also on CVD in patients with type 2 diabetes.

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