

ABSTRACTS

Testosterone

Estrogen production and action.

Estradiol production is most commonly thought of as an endocrine product of the ovary; however, there are many tissues that have the capacity to synthesize estrogens from androgen and to use estrogen in a paracrine or intracrine fashion. In addition, other organs such as the adipose tissue can contribute significantly to the circulating pool of estrogens. There is increasing evidence that in both men and women extraglandular production of C(18) steroids from C(19) precursors is important in normal physiology as well as in pathophysiologic states. The enzyme aromatase is found in a number of human tissues and cells, including ovarian granulosa cells, the placental syncytiotrophoblast, adipose and skin fibroblasts, bone, and the brain, and it locally catalyzes the conversion of C(19) steroids to estrogens. Aromatase expression in adipose tissue and possibly the skin primarily accounts for the extraglandular (peripheral) formation of estrogen and increases as a function of body weight and advancing age. Sufficient circulating levels of the biologically active estrogen estradiol can be produced as a result of extraglandular aromatization of androstenedione to estrone that is subsequently reduced to estradiol in peripheral tissues to cause uterine bleeding and endometrial hyperplasia and cancer in obese anovulatory or postmenopausal women. Extraglandular aromatase expression in adipose tissue and skin (via increasing circulating levels of estradiol) and bone (via increasing local estrogen concentrations) is of paramount importance in slowing the rate of postmenopausal bone loss. Moreover, excessive or inappropriate aromatase expression was demonstrated in adipose fibroblasts surrounding a breast carcinoma, endometriosis-derived stromal cells, and stromal cells in endometrial cancer, giving rise to increased local estrogen concentrations in these tissues. Whether systemically delivered or locally produced, elevated estrogen levels will promote the growth of these steroid-responsive tissues. Finally, local estrogen biosynthesis by aromatase activity in the brain may be important in the regulation of various cognitive and hypothalamic functions. The regulation of aromatase expression in human cells via alternatively used promoters, which can be activated or inhibited by various hormones, increases the complexity of estrogen biosynthesis in the human body. Aromatase expression is under the control of the classically located proximal promoter II in the ovary and a far distal promoter I.1 (40 kilobases upstream of the translation initiation site) in the placenta. In skin, the promoter is I.4. In adipose tissue, 2 other promoters (I.4 and I.3) located between I.1 and II are used in addition to the ovarian-type promoter II. In addition, promoter use in adipose fibroblasts switches between promoters II/I.3 and I.4 upon treatments of these cells with PGE(2) versus glucocorticoids plus cytokines. Moreover, the presence of a carcinoma in breast adipose tissue also causes a switch of promoter use from I.4 to II/I.3. Thus there can be complex mechanisms that regulate the extraglandular production of estrogen in a tissue-specific and state-specific fashion.

J Am Acad Dermatol . 2001 Sep;45(3 Suppl):S116-24

Neuroendocrine aging in men. Andropause and somatopause.

Aging is accompanied by gradual but progressive reductions in the secretion of testosterone and growth hormone in men, and by alterations in body composition and functional capacity that, to some degree, undo the effects of puberty. Preventing or reversing these changes with the use of trophic factors, including androgens, growth hormone, and growth hormone secretagogues, is an appealing prospect, but documenting the effectiveness of these interventions and their benefits and risks has proven to be a difficult undertaking that is far from complete. Small-scale clinical studies have shown that it is practicable to boost growth hormone and IGF-1 levels for periods of up to 12 months, and testosterone for up to 36 months, to reverse at least some age-related changes in body composition. Information regarding the effects of these interventions on strength, exercise capacity, and the ability to perform activities of daily living is still sparse, and additional reports from recently completed or currently ongoing clinical trials will not provide sufficient data to make firm conclusions. From the limited information currently available, androgen supplementation may be of benefit in some men aged more than 65 years, particularly in men with low serum testosterone levels (< 2 ng/mL). In this group, supplemental androgen therapy would be expected to increase lean body mass, bone mass, and possibly strength. In older men with testosterone levels between 2 and 3.5 ng/mL, some benefit might result from androgen supplementation, but it is not yet clear whether the benefits outweigh the risks. For men in this category, one might consider a 6- to 12-month trial of therapy after a full discussion and explicit consent, followed by a reassessment of the value of ongoing treatment. The even more limited data on growth hormone or growth hormone secretagogue interventions in aging do not support their general clinical use in healthy older men. Growth hormone is much more expensive than testosterone and is not covered by insurance for off-label uses. Patients who persistently seek a trial of therapy should be encouraged to enroll in a study if one is locally available. All of the growth hormone studies reported to date have focused, generally for reasons of safety, on healthy and robust groups of older subjects, men in whom the need for intervention is least compelling and in whom the functional effects of treatment may be the most difficult to observe. Phase II studies of intermediate size and duration examining prefrail groups of elderly who are at greater risk for functional loss and who stand to benefit the most from either preventive or restorative

interventions are underway but are limited to the intermediate outcomes of body composition, strength, and function. Trials designed to assess clinically relevant final outcomes, such as falls, fractures, and institutionalization, are of necessity large-scale, long-term, and expensive. Support for larger phase III studies of growth hormone is unlikely to be forthcoming until the phase II studies are completed and show further promise. A multicenter clinical trial of testosterone is currently being planned under the joint sponsorship of the National Institute on Aging, the Veterans Health Administration, and industry, aimed at assessing the effects of testosterone on the risk for falls and fractures. The results of this trial and other large clinical trials should help to better define the balance of benefits and risks of trophic factor intervention in normal older men.

Endocrinol Metab Clin North Am . 2001 Sep;30(3):647-69

Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men.

In the present cross-sectional study of 403 independently living elderly men, we tested the hypothesis that the decreases in bone mass, body composition, and muscle strength with age are related to the fall in circulating endogenous testosterone (T) and estrogen concentrations. We compared various measures of the level of bioactive androgen and estrogen to which tissues are exposed. After exclusion of subjects with severe mobility problems and signs of dementia, 403 healthy men (age, 73-94 yr) were randomly selected from a population-based sample. Total T (TT), free T (FT), estrone (E1), estradiol (E2), and sex hormone-binding globulin (SHBG) were determined by RIA. Levels of non-SHBG-bound T (non-SHBG-T), FT (calc-FT), the TT/SHBG ratio, non-SHBG-bound E2, and free E2 were calculated. Physical characteristics of aging included muscle strength measured using dynamometry, total body bone mineral density (BMD), hip BMD, and body composition, including lean mass and fat mass, measured by dual-energy x-ray absorptiometry. In this population of healthy elderly men, calc-FT, non-SHBG-T, E1, and E2 (total, free, and non-SHBG bound) decreased significantly with age. T (total and non-SHBG-T) was positively related with muscle strength and total body BMD (for non-SHBG-T, respectively, $\beta = 1.93 \pm 0.52$, $P < 0.001$ and $\beta = 0.011 \pm 0.002$, $P < 0.001$). An inverse association existed between T and fat mass ($\beta = -0.53 \pm 0.15$, $P < 0.001$). Non-SHBG-T and calc-FT were more strongly related to muscle strength, BMD, and fat mass than TT and were also significantly related to hip BMD. E1 and E2 were both positively, independently associated with BMD (for E2, $\beta = 0.21 \pm 0.08$, $P < 0.01$). Non-SHBG-bound E2 was slightly strongly related to BMD than total E2. The positive relation between T and BMD was independent of E2. E1 and E2 were not related with muscle strength or body composition. In summary, bioavailable T, E1, total E2, and bioavailable E2 all decrease with age in healthy old men. In this cross-sectional study in healthy elderly men, non-SHBG-bound T seems to be the best parameter for serum levels of bioactive T, which seems to play a direct role in the various physiological changes that occur during aging. A positive relation with muscle strength and BMD and a negative relation with fat mass was found. In addition, both serum E1 and E2 seem to play a role in the age-related bone loss in elderly men, although the cross-sectional nature of the study precludes a definitive conclusion. Non-SHBG-bound E2 seems to be the best parameter of serum bioactive E2 in describing its positive relation with BMD.

J Clin Endocrinol Metab . 2000 Sep;85(9):3276-82

Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis.

To determine the complications, toxicities, and compliance of long term testosterone replacement in hypogonadal males, we retrospectively assessed 45 elderly hypogonadal men receiving testosterone replacement therapy and 27 hypogonadal men taking testosterone. Hypogonadism was defined as a bioavailable testosterone serum concentration of 72 ng/dL or less. Both groups received baseline physical examinations and blood tests. The testosterone-treated group received 200 mg testosterone enanthate or cypionate im every 2 weeks, and follow-up examinations and blood samplings were performed every 3 months. The control group had a single follow-up blood test and physical examination. There was no significant difference in the initial blood tests in the two groups. At 2 yr follow-up, only the hematocrit showed a statistically significant increase in the testosterone-treated group compared to the control group ($P < 0.001$). A decrease in the urea nitrogen to creatinine ratio and an increase in the prostate-specific antigen concentration was not statistically significant. Eleven (24%) of the testosterone-treated subjects developed polycythemia sufficient to require phlebotomy or the temporary withholding of testosterone, one third of which occurred less than 1 yr after starting testosterone treatment. There was no significant difference in the incidence of new illness in the two groups during the 2-yr follow-up. Although self-assessment of libido was dramatically improved in the testosterone-treated group ($P < 0.0001$), approximately one third of the subjects discontinued therapy. In conclusion, testosterone replacement therapy appears to be well tolerated by over 84% of the subjects. Long term testosterone replacement to date appears to be a safe and effective means of treating hypogonadal elderly males, provided that frequent follow-up blood tests and examinations are performed.

J Clin Endocrinol Metab . 1997 Nov;82(11):3793-6

Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group.

Testosterone (T) therapy for hypogonadal men should correct the clinical abnormalities of T deficiency, including improvement of sexual function, increase in muscle mass and strength, and decrease in fat mass, with minimal adverse effects. We have shown that administration of a new transdermal T gel formulation to hypogonadal men provided dose proportional increases in serum T levels to the normal adult male range. We now report the effects of 180 days of treatment with this 1% T gel preparation (50 or

100 mg/day, contained in 5 or 10 g gel, respectively) compared to those of a permeation-enhanced T patch (5 mg/day) on defined efficacy parameters in 227 hypogonadal men. In the T gel groups, the T dose was adjusted up or down to 75 mg/day (contained in 7.5 g gel) on day 90 if serum T concentrations were below or above the normal male range. No dose adjustment was made with the T patch group. Sexual function and mood changes were monitored by questionnaire, body composition was determined by dual energy x-ray absorptiometry, and muscle strength was measured by the one repetitive maximum technique on bench and leg press exercises. Sexual function and mood improved maximally on day 30 of treatment, without differences across groups, and showed no further improvement with continuation of treatment. Mean muscle strength in the leg press exercise increased by 11 to 13 kg in all treatment groups by 90 days and did not improve further at 180 days of treatment. Moderate increases were also observed in arm/chest muscle strength. At 90 days of treatment, lean body mass increased more in the 100 mg/day T gel group (2.74 +/- 0.28 kg; P = 0.0002) than in the 50 mg/day T gel (1.28 +/- 0.32 kg) and T patch groups (1.20 +/- 0.26 kg). Fat mass and percent fat were not significantly decreased in the T patch group, but showed decreases in the T gel groups (50 mg/day, -0.90 +/- 0.32 kg; 100 mg/day, -1.05 +/- 0.22 kg). The increase in lean mass and the decrease in fat mass were correlated with the changes in average serum T levels attained after transdermal T replacement. These beneficial effects of T replacement were accompanied by the anticipated increases in hematocrit and hemoglobin but without significant changes in the lipid profile. The increase in mean serum prostate-specific antigen levels (within the normal range) was correlated with serum levels of T. The greatest increases were noted in the 100 mg/day T gel group. Skin irritation was reported in 5.5% of subjects treated with T gel and in 66% of subjects in the permeation-enhanced T patch group. We conclude that T gel replacement improved sexual function and mood, increased lean mass and muscle strength (principally in the legs), and decreased fat mass in hypogonadal men with less skin irritation and discontinuation compared with the recommended dose of the permeation-enhanced T patch.

J Clin Endocrinol Metab . 2000 Aug;85(8):2839-53.

Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study.

In both men and women, circulating androgen levels decline with advancing age. Until now, results of several small studies on the relationship between endogenous androgen levels and atherosclerosis have been inconsistent. In the population-based Rotterdam Study, we investigated the association of levels of dehydroepiandrosterone sulfate (DHEAS) and total and bioavailable testosterone with aortic atherosclerosis among 1,032 nonsmoking men and women aged 55 yr and over. Aortic atherosclerosis was assessed by radiographic detection of calcified deposits in the abdominal aorta, which have been shown to reflect intimal atherosclerosis. Relative to men with levels of total and bioavailable testosterone in the lowest tertile, men with levels of these hormones in the highest tertile had age-adjusted relative risks of 0.4 [95% confidence interval (CI), 0.2-0.9] and 0.2 (CI, 0.1-0.7), respectively, for the presence of severe aortic atherosclerosis. The corresponding relative risks for women were 3.7 (CI, 1.2-11.6) and 2.3 (CI, 0.7-7.8). Additional adjustment for cardiovascular disease risk factors did not materially affect the results in men, whereas in women the associations diluted. Men with levels of total and bioavailable testosterone in subsequent tertiles were also protected against progression of aortic atherosclerosis measured after 6.5 yr (SD +/- 0.5 yr) of follow-up (P for trend = 0.02). No clear association between levels of DHEAS and presence of severe aortic atherosclerosis was found, either in men or in women. In men, a protective effect of higher levels of DHEAS against progression of aortic atherosclerosis was suggested, but the corresponding test for trend did not reach statistical significance. In conclusion, we found an independent inverse association between levels of testosterone and aortic atherosclerosis in men. In women, positive associations between levels of testosterone and aortic atherosclerosis were largely due to adverse cardiovascular disease risk factors.

J Clin Endocrinol Metab. 2002 Aug;87(8):3632-9.

Transdermal dihydrotestosterone treatment of 'andropause'.

Male ageing coincides on average with progressive impairment of testicular function. The most striking plasma changes are an increase in sex hormone binding globulin (SHBG) and a decrease in non SHBG-bound testosterone, which is the only testosterone subfraction effectively bioavailable for target tissues. In healthy subjects the bioavailable testosterone declines by approximately 1% per year between 40 and 70 years but a more pronounced decline has been observed in non-healthy groups, especially in high cardiovascular risks groups. Relative androgen deficiency is likely to have unfavourable consequences on muscle, adipose tissue, bone, haematopoiesis, fibrinolysis, insulin sensitivity, central nervous system, mood and sexual function and might be treated by an appropriate androgen supplementation. The potential risk for prostate has been the main reason for limiting indications of such treatment. Testosterone (T) and dihydrotestosterone (DHT) are two potent androgens which have opposite effects regarding aromatase activity, an enzyme present in prostate stroma and suspected to have a pathogenic influence through local oestradiol synthesis. T is the main substrate for aromatase and oestradiol synthesis while DHT is not aromatizable and, at sufficient concentration, decreases T and oestradiol levels. A 1.8 years survey of 37 men aged 55-70 years treated with daily percutaneous DHT treatment suggested that high plasma levels of DHT (> 8.5 nmol/l) effectively induced clinical benefits while slightly but significantly reducing prostate size. Early stages of prostate hypertrophy require synergic stimulation by both DHT and oestradiol, and suppressing oestradiol instead of DHT seems easier and better adapted to the specific situation of aged hypogonadic men.

Ann Med . 1993 Jun;25(3):235-41

Antiestrogens and selective estrogen receptor modulators reduce prostate cancer risk.

The development of chemoprevention strategies against prostate cancer would have the greatest overall impact both medically and economically against prostate cancer. Estrogens are required for prostate carcinogenesis. Estrogenic stimulation through estrogen receptor alpha in a milieu of decreasing androgens contributes significantly to the genesis of benign prostatic hyperplasia, prostate dysplasia, and prostate cancer. The ability of antiestrogens and selective estrogen receptor modulators (SERMs) to delay and to suppress prostate carcinogenesis is supported by preclinical, clinical, and epidemiological studies. SERMs have many features that make them attractive candidates for prostate cancer chemoprevention including their favorable safety profile and efficacy in preclinical prostate cancer models. The true clinical benefits of SERMs for chemoprevention to prevent prostate cancer, however, should continue to be investigated through human clinical trials. A phase IIb/III human clinical trial is currently evaluating safety and efficacy of toremifene, a SERM, in men who have high-grade prostatic intraepithelial neoplasia.

World J Urol . 2003 May;21(1):31-6. Epub 2003 Feb 14

Three-year follow-up of androgen treatment in hypogonadal men: preliminary report with testosterone gel.

Transdermal testosterone gels represent an effective alternative to injectable testosterone preparations. Short-term (6 months) data demonstrated positive effects on muscle, bone, fat, libido and mood. This report provides a preliminary analysis of longer-term treatment with a testosterone gel (AndroGel or Testogel) in a group of men aged 19-67 years of age. The positive effects of testosterone treatment on all of the above parameters persisted in this 3-year follow-up. The benefits occurred independent of age (equally in the older and younger subjects). The positive effects of transdermal testosterone gel on bone mineral density previously identified at 6 months of treatment, continued with time. The positive effects on bone mineral density were greater in the spine than the hip. There were minimal effects on lipid levels. Levels of prostate-specific antigen (PSA) increased with testosterone treatment but, in general, remained in the normal range. Three subjects (1.8%) were shown to have elevated PSA and biopsy-proven prostate cancer. It was not possible to determine if this incidence is above the background rate. Monitoring for prostate disease through PSA measurements and digital rectal examination is recommended for hypogonadal men in the older age groups when treated with testosterone.

Aging Male . 2003 Sep;6(3):207-11

Effects of heavy-resistance training on hormonal response patterns in younger vs. older men.

To examine the adaptations of the endocrine system to heavy-resistance training in younger vs. older men, two groups of men (30 and 62 yr old) participated in a 10-wk periodized strength-power training program. Blood was obtained before, immediately after, and 5, 15, and 30 min after exercise at rest before and after training and at rest at -3, 0, 6, and 10 wk for analysis of total testosterone, free testosterone, cortisol, growth hormone, lactate, and ACTH analysis. Resting values for insulin-like growth factor (IGF)-I and IGF-binding protein-3 were determined before and after training. A heavy-resistance exercise test was used to evaluate the exercise-induced responses (4 sets of 10-repetition maximum squats with 90 s of rest between sets). Squat strength and thigh muscle cross-sectional area increased for both groups. The younger group demonstrated higher total and free testosterone and IGF-I than the older men, training-induced increases in free testosterone at rest and with exercise, and increases in resting IGF-binding protein-3. With training the older group demonstrated a significant increase in total testosterone in response to exercise stress along with significant decreases in resting cortisol. These data indicate that older men do respond with an enhanced hormonal profile in the early phase of a resistance training program, but the response is different from that of younger men.

J Appl Physiol . 1999 Sep;87(3):982-92

Effects of strength training on muscle power and serum hormones in middle-aged and older men.

Effects of 16-wk strength training on maximal strength and power performance of the arm and leg muscles and serum concentrations [testosterone (T), free testosterone (FT), and cortisol] were examined in 11 middle-aged (M46; 46 +/- 2 yr) and 11 older men (M64; 64 +/- 2 yr). During the 16-wk training, the relative increases in maximal strength and muscle power output of the arm and leg muscles were significant in both groups ($P < 0.05-0.001$), with no significant differences between the two groups. The absolute increases were higher ($P < 0.01-0.05$) in M46 than in M64 mainly during the last 8 wk of training. No significant changes were observed for serum T and FT concentrations. Analysis of covariance showed that, during the 16-wk training period, serum FT concentrations tended to decrease in M64 and increase in M46 ($P < 0.05$). However, significant correlations between the mean level of individual serum T and FT concentrations and the individual changes in maximal strength were observed in a combined group during the 16-wk training ($r = 0.49$ and 0.5 , respectively; $P < 0.05$). These data indicate that a prolonged total strength-training program would lead to large gains in maximal strength and power load characteristics of the upper and lower extremity muscles, but the pattern of maximal and power development seemed to differ between the upper and lower extremities in both groups, possibly limited in magnitude because of neuromuscular and/or age-related endocrine impairments.

J Appl Physiol . 2001 Apr;90(4):1497-507

Relationships between types of fat consumed and serum estrogen and androgen concentrations in Japanese men.

The relationships between types of fat consumed and serum concentrations of estrone, estradiol, total and free testosterone, dihydrotestosterone, and sex hormone-binding globulin were examined in 69 Japanese men aged 43-88 years. Diet was assessed by a semiquantitative food frequency questionnaire. Intake of saturated, monounsaturated, and polyunsaturated fats was inversely correlated with serum total testosterone after controlling for age, total energy, body mass index, alcohol intake, and smoking status, but the correlation was statistically significant only for polyunsaturated fat ($r = -0.29$, $p = 0.02$). Intakes of eicosapentanoic and docosahexaenoic acids, n-3 fatty acids from fish, were significantly inversely correlated with total testosterone ($r = -0.25$, $p = 0.04$ and $r = -0.32$, $p = 0.01$, respectively). Serum estrone, estradiol, and free testosterone were not significantly correlated with any type of fat studied. The correlations of total testosterone with n-3 fatty acids from fish remained significant after additional adjustment for the other categories of fat ($r = -0.27$, $p = 0.03$ for eicosapentanoic acid and $r = -0.32$, $p = 0.01$ for docosahexaenoic acid), while the correlations with saturated and monounsaturated fats became nearly null after the adjustment.

Nutr Cancer . 2000;38(2):163-7

ABSTRACTS

Liver disease

Nonalcoholic steatohepatitis.

Nonalcoholic steatohepatitis (NASH) is a condition characterized by hepatomegaly, elevated serum aminotransferase levels, and a histologic picture similar to alcoholic hepatitis in the absence of alcohol abuse. Most patients with NASH are obese women, and many have diabetes mellitus, hypercholesterolemia, or hypertriglyceridemia. NASH has also been associated with a number of metabolic conditions, surgical procedures, and drug treatments. Most patients are asymptomatic. The most common sign of NASH is hepatomegaly. Stigmata of chronic liver disease are rare. Laboratory abnormalities include a 2-4-fold elevation of serum aminotransferase levels; other liver function test results are usually normal. Histologically, there is moderate to severe macrovesicular steatosis and lobular hepatitis with necrosis or ballooning degeneration and/or fibrosis. The pathogenesis of NASH is poorly understood, but lipid peroxidation and oxidative stress are the leading culprits. The natural history of NASH is unknown, but NASH seems to be a stable disease in most patients. Treatment of NASH is unproven, but weight reduction is recommended in obese patients. Small pilot studies of several drugs have shown promise, but large randomized clinical trials are awaited. Orthotopic liver transplantation is the treatment of choice for end-stage liver disease secondary to NASH.

Gastroenterology . 2001 Sep;121(3):710-23

Polyenylphosphatidylcholine inhibits PDGF-induced proliferation in rat hepatic stellate cells.

Polyenylphosphatidylcholine (PPC), a polyunsaturated phospholipid extract from soy beans, prevents the development of liver cirrhosis in animal models. Its mechanism of action is unknown. Based on the hypothesis that PPC might act by decreasing hepatic stellate cell proliferation, we studied the effect of PPC and its main components, dilinoleoylphosphatidylcholine (DLPC) and palmitoyl-linoleoylphosphatidylcholine (PLPC), on PDGF-induced stellate cell proliferation and intracellular signal transduction. Normal rat hepatic stellate cells in tissue culture were serumstarved, and incubated with 10ng/ml PDGF in the absence or presence of phospholipids. Cell proliferation was measured by 3H-thymidine incorporation. P44MAPK activation was determined by kinase assay, and AP-1 binding by electrophoretic mobility shift assay. PPC (200 ng/ml) significantly inhibited PDGF-induced proliferation ($p < 0.05$; ANOVA, $n = 3$) and antagonized PDGF-induced P44MAPK activation and AP-1 binding. This effect was mimicked by DLPC but not by PLPC. Neither DLPC nor PLPC prevented PDGF receptor activation. We conclude that PPC exerts a previously unrecognized effect on mitogen-induced stellate cell proliferation which may be mediated by DLPC. Inhibition of this cascade represents a potential mechanism for the inhibitory effect of PPC on hepatic fibrogenesis.

Biochem Biophys Res Commun . 1998 Jul 9;248(1):174-9

Nonalcoholic steatohepatitis in children.

Nonalcoholic steatohepatitis (NASH) is one entity in a spectrum of chronic liver disease related to obesity, hyperinsulinemia, insulin resistance, and liver cell injury from free fatty acid toxicity or other oxidant stress. The more inclusive term "nonalcoholic fatty liver disease" (NAFLD) is increasingly being used to encompass the entire spectrum, which includes simple hepatic steatosis without inflammation (which may not lead to progressive liver injury), NASH itself, and the resulting cirrhosis (which may be devoid of steatosis). Children get NAFLD, and the incidence of this pediatric liver disease is rising as childhood obesity becomes increasingly prevalent. Although much remains to be learned about pediatric NAFLD, it is already evident that children with NASH risk progressive liver damage, including cirrhosis. Liver biopsy is required for definitive diagnosis, and other causes of fatty liver in childhood must be excluded. Gradual weight loss through increased regular exercise and a low-fat, low-refined carbohydrate diet appears to be effective. Drug treatments are being developed. Pediatric NASH is a serious complication of childhood obesity.

Curr Gastroenterol Rep . 2003 Jun;5(3):253-9

Nonalcoholic fatty liver disease (NAFLD) in children.

Nonalcoholic fatty liver disease (NAFLD) is common in obese children and is a growing problem, given the increase in prevalence of obesity. NAFLD is also associated with diabetes, insulin resistance, hypercholesterolemia, and hypertriglyceridemia. Although mostly benign, some children with NAFLD develop fibrosis and cirrhosis, which necessitates close monitoring. Chronically elevated plasma liver enzyme levels is the most frequent finding. Ultrasound (US) examination allows confirmation of the diagnosis and it is useful for the follow-up. Gradual and sustained weight reduction is a management option that is worth trying initially. Other modalities of management, although interesting, await evidence as well as information on long-term benefits and effects. Sustained increase of transaminases despite weight reduction is a cause for concern and may require a liver biopsy both to assess severity of liver damage and for prognostic purposes.

Curr Opin Pediatr . 2002 Oct;14(5):593-600

Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.

Nonalcoholic steatohepatitis is a poorly understood and hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis. Described here are findings in 20 patients with nonalcoholic steatohepatitis of unknown cause. The biopsy specimens were characterized by the presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates, and, in most instances, Mallory bodies; Evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed in biopsy tissue from three patients. The disease was more common in women. Most patients were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus and cholelithiasis. Presence of hepatomegaly and mild abnormalities of liver function were common clinical findings. Currently, we know of no effective therapy.

Mayo Clin Proc . 1980 Jul;55(7):434-8

Motion - all patients with NASH need to have a liver biopsy: arguments against the motion.

Most cases of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are suspected on the basis of the exclusion of viral, autoimmune, metabolic and genetic causes of chronic liver disease in patients with chronic elevation of aminotransferase enzymes. However, the definitive diagnosis of NASH requires liver biopsy. Valuable blood tests include hepatitis B and C serology, iron profile, alpha 1-antitrypsin phenotype, ceruloplasmin, antinuclear antibody and antismooth muscle antibody, and serum protein electrophoresis. If these tests are negative or normal, and if there are no symptoms or signs of chronic liver disease, it is unlikely that a specifically treatable liver disease would be discovered at biopsy. The prevalence of NAFLD in the general population appears to be approximately 20%, and 2% to 3% of people have NASH. There is no proven specific therapy for the spectrum of nonalcoholic liver disease; therefore, the management of the patient with NASH is not likely to be changed after histological assessment. Bleeding, sometimes fatal, and other complications requiring hospitalization can occur, and liver biopsies should not be undertaken without clear clinical indications. The high cost of undertaking histological assessment of all persons with asymptomatic elevations of liver enzymes cannot be justified in view of the risks and limited clinical benefits.

Can J Gastroenterol . 2002 Oct;16(10):722-6

The utility of radiological imaging in nonalcoholic fatty liver disease.

BACKGROUND & AIMS: This prospective study evaluates the role of radiological modalities in establishing the diagnosis of nonalcoholic steatohepatitis (NASH). **METHODS:** Consecutive patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD) were enrolled (2000-2001). Patients with other liver diseases and significant alcohol consumption (>20 g/day) were excluded. Clinicodemographic data were gathered at the time of liver biopsy. Each biopsy specimen was assessed by a hepatopathologist. Each patient underwent a limited abdominal ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI). Films were interpreted by a radiologist who used a predetermined radiological protocol. Each radiological study was reread by the same radiologist and a second radiologist. **RESULTS:** Patients with NASH had greater aspartate aminotransferase levels (P = 0.03), greater ferritin levels (P = 0.05), more hepatocyte ballooning (P < 0.0001), and more fibrosis (P = 0.002). None of the radiological features distinguished between NASH and other types of NAFLD. No radiological modality detected the presence of hepatocyte ballooning, Mallory's hyaline, or fibrosis, which are important features in the diagnosis of NASH. The presence of >33% fat on liver biopsy was optimal for detecting steatosis on radiological imaging. **CONCLUSIONS:** Differences between NASH and nonprogressive NAFLD were not apparent with any radiological modality. Of the pathologic features important for establishing the diagnosis of NASH, only the severity of steatosis was reflected in these radiological modalities. Good intraobserver agreement was evident for each modality (US, CT, and MRI) that was superior to interobserver agreement.

Gastroenterology. 2002 Sep;123(3):745-50

CT and MRI of diffuse liver disease.

CT and MRI contribute important information to the clinical evaluation of diffuse liver disease. In some cases, these modalities can establish a diagnosis that was not ascertained histologically, which is often the case when sampling errors prevent a definitive tissue diagnosis. Characteristic alterations of liver attenuation on CT, signal changes on MRI, and morphological changes appreciated with both modalities can be used to diagnose fatty infiltration, some parenchymal deposition diseases, and cirrhosis. Furthermore, hepatocellular disease can be confirmed in the setting of indeterminate clinical and laboratory findings. Significant overlap in the imaging findings of this wide range of disorders continues to limit specificity; however, at a minimum, these techniques provide a rapid means to a noninvasive evaluation that often guides clinical decisions. Faster scanning techniques available with CT and MRI may provide additional information by assessing contrast dynamics. This review of CT and MRI in diffuse liver disease considers the diagnostic utility and clinical implications of these modalities. Pathological findings relevant to imaging considerations are discussed.

Semin Ultrasound CT MR. 1995 Feb;16(1):16-33

Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values.

A retrospective study was performed to (1) characterize the clinical and histologic features of those with nonalcoholic fatty liver disease (NAFLD) and normal alanine aminotransferase (ALT) values, (2) compare the spectrum of NAFLD associated with normal versus elevated ALT levels, and (3) determine whether there were differences in the clinical or histologic spectrum of NAFLD between those with a low normal versus high normal ALT value. A total of 51 subjects with NAFLD and normal ALT were identified and compared with 50 consecutive subjects with NAFLD and elevated ALT. The major indications for liver biopsy in those with normal ALT were unexplained hepatomegaly (n = 21) and evaluation as a potential donor for living donor liver transplantation (n = 16). The 2 groups were comparable with respect to age, gender distribution, and ethnicity. Approximately 80% of cases in both groups had at least 1 feature of the metabolic syndrome, the major risk factor for NAFLD. The 2 groups were also comparable with respect to the grade of the individual histologic parameters of NAFLD. A total of 12 subjects with normal ALT levels had bridging fibrosis, whereas 6 had cirrhosis. Diabetes was the only factor independently associated with an increased risk of advanced fibrosis (bridging fibrosis or cirrhosis) by multivariate analysis (relative risk: 2.3, P <.01). The mean steatosis (1.6 vs. 2.16, P <.04) and perisinusoidal fibrosis scores (0.35 vs. 0.9, P <.049) were lower in those with low normal (<30 IU/L) ALT versus high normal ALT. However, the prevalence of advanced fibrosis was similar (5 of 15 vs. 13 of 36, respectively). In conclusion, (1) the entire histologic spectrum of NAFLD can be seen in individuals with normal ALT values, (2) the histologic spectrum in these individuals is not significantly different from those with elevated ALT levels, and (3) a low normal ALT value does not guarantee freedom from underlying steatohepatitis with advanced fibrosis.

Hepatology . 2003 Jun;37(6):1286-92

Creatine

Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis.

The purpose of this study was to quantify which dietary supplements augment lean mass and strength gains during resistance training. Peer-reviewed studies between the years 1967 and 2001 were included in the analysis if they met a predetermined set of experimental criteria, among which were at least 3-wk duration and resistance-training 2 or more times a week. Lean mass and strength were normalized for meta-analysis by conversion to percent change per week and by calculating the effect size for each variable. Of the 250 supplements examined, only 6 had more than 2 studies that met the criteria for inclusion in the meta-analysis. Creatine and beta-hydroxy-beta-methylbutyrate (HMB) were found to significantly increase net lean mass gains of 0.36 and 0.28%/wk and strength gains of 1.09 and 1.40%/wk (P < 0.05), respectively. Chromium, dehydroepiandrosterone, androstenedione, and protein did not significantly affect lean gain or strength. In conclusion, two supplements, creatine and HMB, have data supporting their use to augment lean mass and strength gains with resistance training.

J Appl Physiol . 2003 Feb;94(2):651-9. Epub 2002 Oct 25

Effects of creatine supplementation on performance and training adaptations.

Creatine has become a popular nutritional supplement among athletes. Recent research has also suggested that there may be a number of potential therapeutic uses of creatine. This paper reviews the available research that has examined the potential ergogenic value of creatine supplementation on exercise performance and training adaptations. Review of the literature indicates that over 500 research studies have evaluated the effects of creatine supplementation on muscle physiology and/or exercise capacity in healthy, trained, and various diseased populations. Short-term creatine supplementation (e.g. 20 g/day for 5-7 days) has typically been reported to increase total creatine content by 10-30% and phosphocreatine stores by 10-40%. Of the approximately 300 studies that have evaluated the potential ergogenic value of creatine supplementation, about 70% of these studies report statistically significant results while remaining studies generally report non-significant gains in performance. No study reports a statistically significant ergolytic effect. For example, short-term creatine supplementation has been reported to improve maximal power/strength (5-15%), work performed during sets of maximal effort muscle contractions (5-15%), single-effort sprint performance (1-5%), and work performed during repetitive sprint performance (5-15%). Moreover, creatine supplementation during training has been reported to promote significantly greater gains in strength, fat free mass, and performance primarily of high intensity exercise tasks. Although not all studies report significant results, the preponderance of scientific evidence indicates that creatine supplementation appears to be a generally effective nutritional ergogenic aid for a variety of exercise tasks in a number of athletic and clinical populations.

Mol Cell Biochem . 2003 Feb;244(1-2):89-94

Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease?

Major achievements made over the last several years have highlighted the important roles of creatine and the creatine kinase reaction in health and disease. Inborn errors of metabolism have been identified in the three main steps involved in creatine metabolism: arginine:glycine amidinotransferase (AGAT), S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase (GAMT), and the creatine transporter. All these diseases are characterized by a lack of creatine and phosphorylcreatine in the brain, and by (severe) mental retardation. Similarly, knockout mice lacking the brain cytosolic and mitochondrial isoenzymes of creatine kinase displayed a slightly increased creatine concentration, but no phosphorylcreatine in the brain. These mice revealed decreased weight gain and reduced life expectancy, disturbed fat metabolism, behavioral abnormalities and impaired

learning capacity. Oral creatine supplementation improved the clinical symptoms in both AGAT and GAMT deficiency, but not in creatine transporter deficiency. In addition, creatine supplementation displayed neuroprotective effects in several animal models of neurological disease, such as Huntington's disease, Parkinson's disease, or amyotrophic lateral sclerosis. All these findings pinpoint to a close correlation between the functional capacity of the creatine kinase/phosphorylcreatine/creatine system and proper brain function. They also offer a starting-point for novel means of delaying neurodegenerative disease, and/or for strengthening memory function and intellectual capabilities. Finally, creatine biosynthesis has been postulated as a major effector of homocysteine concentration in the plasma, which has been identified as an independent graded risk factor for atherosclerotic disease. By decreasing homocysteine production, oral creatine supplementation may, thus, also lower the risk for developing, e.g., coronary heart disease or cerebrovascular disease. Although compelling, these results require further confirmation in clinical studies in humans, together with a thorough evaluation of the safety of oral creatine supplementation.

Neuroscience . 2002;112(2):243-60

Direct antioxidant properties of creatine.

Creatine is the most popular supplement proposed to be an ergogenic aid. There is some evidence in the literature that creatine supplementation increases lean body mass, muscular strength, and sprint power. However, the efficacy of creatine has not been consistent, and the potential mechanisms are unresolved. While limited evidence that suggests that creatine could possess an antioxidant effect this has not been tested directly. Because oxidants such as free radicals can affect muscle fatigue and protein turnover, it is important to know whether creatine can neutralize free radicals and other reactive oxygen species. We tested the hypothesis that creatine would remove superoxide anions ($O^{*-}(2)$), peroxynitrite (OONO-), hydrogen peroxide, and lipid peroxides (t-butyl hydroperoxide). We also determined whether creatine displayed a significant antioxidant scavenging capacity (ASC) using 2,2'-azino-bis(3-ethylbenzothiazolamine-6-sulfonic acid) (ABTS+) quenching as a marker. Creatine did not significantly reduce levels of hydrogen peroxide or lipid peroxidation. In contrast, creatine displayed a significant ability to remove ABTS+, $O^{*-}(2)$, and OONO- when compared with controls. Creatine quenching of ABTS+ was less than physiological levels of reduced glutathione (0.375 mM). To our knowledge, this is the first evidence that creatine has the potential to act as a direct antioxidant against aqueous radical and reactive species ions.

Biochem Biophys Res Commun . 2002 Jan 11;290(1):47-52

Mitochondria, oxidative damage, and inflammation in Parkinson's disease.

The pathogenesis of Parkinson's disease (PD) remains obscure, but there is increasing evidence that impairment of mitochondrial function, oxidative damage, and inflammation are contributing factors. The present paper reviews the experimental and clinical evidence implicating these processes in PD. There is substantial evidence that there is a deficiency of complex I activity of the mitochondrial electron transport chain in PD. There is also evidence for increased numbers of activated microglia in both PD postmortem tissue as well as in animal models of PD. Impaired mitochondrial function and activated microglia may both contribute to oxidative damage in PD. A number of therapies targeting inflammation and mitochondrial dysfunction are efficacious in the MPTP model of PD. Of these, coenzyme Q(10) appears to be particularly promising based on the results of a recent phase 2 clinical trial in which it significantly slowed the progression of PD.

Ann N Y Acad Sci . 2003 Jun;991:120-31

Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders.

Substantial evidence indicates that bioenergetic dysfunction plays either a primary or secondary role in the pathophysiology of cell death in neurodegenerative and neuromuscular disorders, and even in normal aging. Agents that ameliorate bioenergetic defects may therefore be useful in therapy. Creatine, which increases muscle and brain phosphocreatine concentrations, and may inhibit the activation of the mitochondrial permeability transition, protects against neuronal degeneration in transgenic murine models of amyotrophic lateral sclerosis and Huntington's disease and in chemically mediated neurotoxicity. Initial studies of creatine use in humans appear promising; however, further long-term, well-designed trials are needed. Coenzyme Q10, Gingko biloba, nicotinamide, riboflavin, carnitine, lipoic acid, and dichloroacetate are other agents which may have beneficial effects on energy metabolism, but the preclinical and clinical evidence for efficacy in neurological diseases remains limited. These compounds are widely used as dietary supplements; however, they must be subjected to rigorous evaluation through randomized, double-blinded trials to establish efficacy, cost-effectiveness and safety in neurological disorders.

Ann Neurol . 2001 May;49(5):561-74

disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.