

LE Magazine August 2002

ABSTRACTS

Atherosclerosis

Plasma level of homocysteine is inversely-associated with the development of collateral circulation in patients with single-vessel coronary artery disease.

Homocysteine induces endothelial injury and inhibits endothelial cell proliferation, which is a key role in angiogenesis. The purpose of this study was to investigate whether the plasma level of homocysteine is associated with the development of collaterals in patients with single-vessel coronary artery disease (CAD). Among a series of 105 male patients with angiographic estimation, 49 with single-vessel CAD were intensively investigated. Development of collaterals was classified by Rentrop's method. Univariate and multivariate analyses revealed that hyperhomocysteinemia negatively affected the development of collaterals ($p=0.0015$ and 0.0011 , odds ratio 0.69, 95% confidence interval 0.52-0.90), whereas the duration of angina and percent stenosis evaluated by quantitative coronary angiography had a positive affect. Moreover, the level of homocysteine in the group with poorly developed collaterals ($n=7$, Rentrop class 0 and 1) was significantly higher than that in the group with well-developed collaterals ($n=12$, Rentrop class 2 and 3) of the patients with single-vessel disease showing total occlusion ($p=0.034$). This study clearly demonstrates that the plasma level of homocysteine is independently and inversely associated with the development of collateral circulation in CAD patients. Homocysteine might be a new undesirable aspect of ischemic heart disease through its inhibition of collateral development.

Circ J 2002 Feb;66(2):158-62

Risk factors for progression of aortic atheroma in stroke and transient ischemic attack patients.

BACKGROUND AND PURPOSE: Aortic atheroma is an independent risk factor for stroke and undergoes temporal progression. Clinical and risk factor associations of such progression are unknown. Hyperhomocysteinemia has been linked with atherosclerosis, including that in the cerebral vasculature. This study investigated associations between elevated homocysteine levels and other stroke vascular risk factors and the risk of aortic atheroma progression in patients with cerebrovascular disease. **METHODS:** Fifty-seven stroke and 21 transient ischemic attack patients underwent multiplanar transesophageal echocardiograms within one month of symptom onset and again at nine months. Aortic atheroma was graded and stratified by use of existing criteria. Stroke risk factors; use of anticoagulant, antiplatelet and hypolipidemic drugs; and clinical and etiological subtypes of stroke were recorded and compared in patients stratified for the presence or absence of aortic atheroma progression. **RESULTS:** Of the 78, 29 (37%) progressed, 32 (41%) remained unchanged, and 17 (22%) regressed. Progression was most marked at the aortic arch ($P=0.005$), followed by the ascending segment ($P<0.04$). In nearly two-thirds of the patients in whom aortic atheroma remained unchanged over nine months, no atheroma was evident on baseline transesophageal echocardiogram. Only homocysteine levels $> \text{or } =14.0$ micromol/L ($P=0.02$), total anterior cerebral infarct ($P=0.02$), and large-artery atherosclerosis ($P=0.005$) significantly correlated with progression. **CONCLUSIONS:** Among vascular risk factors, elevated homocysteine levels are associated with aortic atheroma progression. Stroke and transient ischemic attack patients with aortic atheroma should undergo assessment of homocysteine levels, which, if elevated, may be treated with vitamins in an effort to arrest aortic atheroma progression.

Stroke 2002 Apr;33(4):930-5

CLA/Weight Loss

Efficacy of dietary CLA and CLA+Guarana (ADIPILL) on body adiposity, and adipocytes cell number and size.

We have compared in mice the effect of a dietary supplementation with either conjugated linoleic acids (CLA) or CLA and guarana (CLA-G) on adiposity. After six weeks, mice were sacrificed and all fat pads were removed and adipocytes number and size were measured in subcutaneous (SCAT) and gonadal (GAT) fat pad. CLA as well as CLA-G supplementation induced a strong lipotrophy, fat mass showing a three-fold decrease in both groups. This effect was more pronounced in gonadal than in subcutaneous site, GAT being reduced 10 times and SCAT four times. Plasma leptin was decreased in CLA and CLA-G treated mice by 40% and 55% respectively. In the CLA group, the decreased fat mass was due to dramatic reduction in adipocyte size without change in cell number. In the CLA-G group, both adipocyte size and number were reduced (-50%). These results demonstrate that dietary CLA are able to decrease adiposity by reducing its capacity to store lipids without affecting adipocyte differentiation. When guarana is added to CLA, an additional effect of cell number is induced. The mechanisms underlying this effect

(cell differentiation/apoptosis) and its potential in preventing body fat accretion in the long-term remain to be investigated.

Experimental Biology Meeting, New Orleans. April 20-24, 2002.

The efficacy of conjugated linoleic acid in mammary cancer prevention is independent of the level or type of fat in the diet.

The objective of the present study was to investigate whether the anticarcinogenic activity of conjugated linoleic acid (CLA) is affected by the amount and composition of dietary fat consumed by the host. Because the anticancer agent of interest is a fatty acid, this approach may provide some insight into its mechanism of action, depending on the outcome of these fat feeding experiments. For the fat level experiment, a custom formulated fat blend was used that simulates the fatty acid composition of the U.S. diet. This fat blend was present at 10, 13.3, 16.7 or 20% by weight in the diet. For the fat type experiment, a 20% (w/w) fat diet containing either corn oil (exclusively) or lard (predominantly) was used. Mammary cancer prevention by CLA was evaluated using the rat dimethylbenz[a]anthracene model. The results indicated that the magnitude of tumor inhibition by 1% CLA was not influenced by the level or type of fat in the diet. It should be noted that these fat diets varied markedly in their content of linoleate. Fatty acid analysis showed that CLA was incorporated predominantly in mammary tissue neutral lipids, while the increase in CLA in mammary tissue phospholipids was minimal. Furthermore, there was no evidence that CLA supplementation perturbed the distribution of linoleate or other fatty acids in the phospholipid fraction. Collectively these carcinogenesis and biochemical data suggest that the cancer preventive activity of CLA is unlikely to be mediated by interference with the metabolic cascade involved in converting linoleic acid to eicosanoids. The hypothesis that CLA might act as an antioxidant was also examined. Treatment with CLA resulted in lower levels of mammary tissue malondialdehyde (an end product of lipid peroxidation), but failed to change the levels of 8-hydroxydeoxyguanosine (a marker of oxidatively damaged DNA). Thus, while CLA may have some antioxidant function in vivo in suppressing lipid peroxidation, its anticarcinogenic activity cannot be accounted for by protecting the target cell DNA against oxidative damage. The finding that the inhibitory effect of CLA maximized at 1% (regardless of the availability of linoleate in the diet) could conceivably point to a limiting step in the capacity to metabolize CLA to some active product(s) which is essential for cancer prevention.

Carcinogenesis 1996 May;17(5):1045-50

Protection of conjugated linoleic acids against 2-amino-3-methylimidazo[4,5-f]quinoline-induced colon carcinogenesis in the F344 rat: a study of inhibitory mechanisms.

Grilled ground beef contains a number of heterocyclic amine carcinogens, such as 2-amino-3-methylimidazo[4,5-f] quinoline (IQ), as well as anticarcinogenic conjugated linoleic acids (CLA). In the present study, CLA was administered to male F344 rats by gavage on alternating days in weeks 1-4, while IQ was given by gavage every other day in weeks 3 and 4 (100 mg/kg body wt). Rats were killed 6 h after the final carcinogen dose in order to score colonic aberrant crypt foci (ACF). In the ACF study, CLA had no effect on the size of the foci, but inhibited significantly ($P < 0.05$) the number of ACF/colon, from 4.3 ± 2.4 in controls to 1.1 ± 1.3 in CLA-treated rats (mean \pm SD, $n = 10$). Rats given CLA also had significantly lower IQ-DNA adducts in the colon as determined by ^{32}P -postlabeling analysis; relative adduct labeling levels (RAL $\times 10^7$) for the major adduct were 9.13 ± 2.6 in controls versus 5.42 ± 1.8 in CLA-treated animals ($P < 0.05$). Mechanism studies indicated that CLA and other fatty acids interact with certain heterocyclic amines in a manner consistent with substrate-ligand binding. However, no such interaction occurred with IQ, and CLA failed to inhibit significantly the mutagenicity of N-hydroxy-IQ in the Salmonella assay. Liver microsomes from CLA-treated rats exhibited lower activities for dealkylation of 7-ethoxyresorufin and methoxyresorufin and activated IQ to DNA binding species less effectively than microsomes from control animals. Direct addition of CLA to the in vitro incubation inhibited IQ-DNA binding and was associated with increased recovery of unmetabolized parent compound. In the Salmonella assay, CLA inhibited the mutagenic activity of IQ in the presence of S9 or ram seminal vesicle microsomes. Collectively, these results support a mechanism involving inhibition of carcinogen activation by CLA, as opposed to direct interaction with the procarcinogen, scavenging of electrophiles or selective induction of phase I detoxification pathways.

Carcinogenesis 1995 Dec;16(12):3037-43

Conjugated dienoic linoleate: a polyunsaturated fatty acid with unique chemoprotective properties.

Conjugated dienoic linoleate (CLA), a linoleic acid derivative, has received considerable attention as a chemoprotective agent in the past few years because it has been shown experimentally to inhibit rat mammary tumorigenesis, mouse forestomach neoplasia and mouse skin carcinogenesis. CLA has several unique structural and functional properties resulting in chemical and physiological effects that are different from those of all-cis, nonconjugated polyunsaturated fatty acids. In turn, these unique qualities appear to modulate cellular processes involved in carcinogenesis. This review will introduce the chemical background of conjugated dienoic linoleate, examine findings describing its chemoprotective qualities, present possible mechanisms of chemoprotection, and correlate the possible significance of dietary CLA modulation to carcinogenesis to humans.

Nutr Rev 1995 Apr;53(4 Pt 1):83-9

Dietary conjugated linoleic acid normalizes impaired glucose tolerance in the Zucker diabetic fatty fa/fa rat.

Conjugated linoleic acid (CLA) is a naturally occurring fatty acid which has anti-carcinogenic and anti-atherogenic properties. CLA activates PPAR alpha in liver, and shares functional similarities to ligands of PPAR gamma, the thiazolidinediones, which are potent insulin sensitizers. We provide the first evidence that CLA is able to normalize impaired glucose tolerance and improve hyperinsulinemia in the pre-diabetic ZDF rat. Additionally, dietary CLA increased steady state levels of aP2 mRNA in adipose tissue of fatty ZDF rats compared to controls, consistent with activation of PPAR gamma. The insulin sensitizing effects of CLA are due, at least in part, to activation of PPAR gamma since increasing levels of CLA induced a dose-dependent transactivation of PPAR gamma in CV-1 cells cotransfected with PPAR gamma and PPRE X 3-luciferase reporter construct. CLA effects on glucose tolerance and glucose homeostasis indicate that dietary CLA may prove to be an important therapy for the prevention and treatment of non-insulin-dependent diabetes mellitus (NIDDM).

Biochem Biophys Res Commun 1998 Mar 27;244(3):678-82

Continued on Page 2 of 4

[Back to the Magazine Forum](#)

ABSTRACTS

Influence of conjugated linoleic acid (CLA) on establishment and progression of atherosclerosis in rabbits.

OBJECTIVE: To determine effects of conjugated linoleic acid (CLA) on the establishment and progression of experimentally-induced atherosclerosis in rabbits. **METHODS:** For establishment of atherosclerosis, New Zealand White rabbits were fed a semipurified diet containing 0.1% to 0.2% cholesterol for 90 days. Some groups were fed diet and CLA. For effects on progression of atherosclerosis, rabbits with established atherosclerosis were fed a semipurified diet +/- CLA for 90 days. **RESULTS:** At dietary levels as low as 0.1%, CLA inhibited atherogenesis. At dietary levels of 1%, CLA caused substantial (30%) regression of established atherosclerosis. This is the first example of substantial regression of atherosclerosis being caused by diet alone. **CONCLUSION:** Dietary CLA is an effective inhibitor of atherogenesis and also causes regression of established atherosclerosis.

J Am Coll Nutr 2000 Aug;19(4):472S-477S

Effect of conjugated linoleic acid on body composition in mice.

The effects of conjugated linoleic acid (CLA) on body composition were investigated. ICR mice were fed a control diet containing 5.5% corn oil or a CLA-supplemented diet (5.0% corn oil plus 0.5% CLA). Mice fed CLA-supplemented diet exhibited 57% and 60% lower body fat and 5% and 14% increased lean body mass relative to controls ($P < 0.05$). Total carnitine palmitoyltransferase activity was increased by dietary CLA supplementation in both fat pad and skeletal muscle; the differences were significant for fat pad of fed mice and skeletal muscle of fasted mice. In cultured 3T3-L1 adipocytes CLA treatment (1×10^{-4} M) significantly reduced heparin-releasable lipoprotein lipase activity (-66%) and the intracellular concentrations of triacylglyceride (-8%) and glycerol (-15%), but significantly increased free glycerol in the culture medium (+22%) compared to control ($P < 0.05$). The effects of CLA on body composition appear to be due in part to reduced fat deposition and increased lipolysis in adipocytes, possibly coupled with enhanced fatty acid oxidation in both muscle cells and adipocytes.

Lipids 1997 Aug;32(8):853-8

Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: a randomized controlled trial.

BACKGROUND: Abdominal obesity is strongly related to metabolic disorders. Recent research suggests that dietary conjugated linoleic acid (CLA) reduces body fat and may improve metabolic variables in animals. The metabolic effects of CLA in abdominally obese humans have not yet been tested. **OBJECTIVE:** To investigate the short-term effect of CLA on abdominal fat and cardiovascular risk factors in middle-aged men with metabolic disorders. **METHODS:** Twenty-five abdominally obese men (waist-to-hip ratio (WHR), 1.05 ± 0.05 ; body mass index (BMI), 32 ± 2.7 kg/m² (mean \pm s.d.)) who were between 39 and 64-y-old participated in a double-blind randomised controlled trial for 4 weeks. Fourteen men received 4.2 g CLA/day and 10 men received a placebo. The main endpoints were differences between the two groups in sagittal abdominal diameter (SAD), serum cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, free fatty acids, glucose and insulin. **RESULTS:** At baseline, there were no significant differences between groups in anthropometric or metabolic variables. After four weeks there was a significant decrease in SAD (cm) in the CLA group compared to placebo ($P=0.04$, 95% CI; -1.12, -0.02). Other measurements of anthropometry or metabolism showed no significant differences between the groups. **CONCLUSIONS:** These results indicate that CLA supplementation for four weeks in obese men with the metabolic syndrome may decrease abdominal fat, without concomitant effects on overall obesity or other cardiovascular risk factors. Because of the limited sample size, the effects of CLA in abdominal obesity need to be further investigated in larger trials with longer duration.

Int J Obes Relat Metab Disord 2001 Aug;25(8):1129-35

Effects of conjugated linoleic acid on body fat and energy metabolism in the mouse.

Conjugated linoleic acid (CLA) is a naturally occurring group of dienoic derivatives of linoleic acid found in the fat of beef and other ruminants. CLA is reported to have effects on both tumor development and body fat in animal models. To further characterize the metabolic effects of CLA, male AKR/J mice were fed a high-fat (45 kcal%) or low-fat (15 kcal%) diet with or without CLA (2.46 mg/kcal; 1.2% and 1.0% by weight in high- and low-fat diets, respectively) for six weeks. CLA significantly reduced energy intake, growth rate, adipose depot weight, and carcass lipid and protein content independent of diet composition. Overall, the reduction of adipose depot weight ranged from 43% to 88%, with the retroperitoneal depot most sensitive to CLA. CLA significantly increased metabolic rate and decreased the nighttime respiratory quotient. These findings demonstrate that CLA reduces body fat by several mechanisms, including a reduced energy intake, increased metabolic rate, and a shift in the nocturnal fuel mix.

Dietary conjugated linoleic acids increase lean tissue and decrease fat deposition in growing pigs.

Conjugated linoleic acid (CLA) decreases the body fat content of rodents. The aim of this study was to determine whether dietary CLA altered carcass composition of pigs. Female Large White x Landrace pigs (n = 66) were used in this study. To obtain initial body composition, six pigs were slaughtered at 57 kg live weight, whereas the remaining pigs were allocated to one of six dietary treatments (0, 1.25, 2.5, 5.0, 7.5 and 10.0 g/kg CLA, containing 55% of CLA isomers). The diets, containing 14.3 MJ digestible energy (DE) and 9.3 g available lysine per kg, were fed ad libitum for eight weeks. Dietary CLA had no significant effect on average daily gain (861 vs. 911 g/d for pigs fed diets with and without CLA, P = 0.15) or feed intake (2.83 vs. 2.80 kg/d, P = 0.74). The gain to feed ratio was increased by dietary CLA by 6.3% (0.328 vs. 0.348, P = 0.009). Fat deposition decreased linearly (-8.2 +/- 2.09 g/d for each gram per kilogram increase in CLA concentration; P < 0.001) with increasing inclusion of CLA. At the highest level of CLA inclusion, fat deposition was decreased by 88 g/d (-31%). Similarly, the ratio of fat to lean tissue deposition decreased linearly (-0.093 +/- 0.0216 for each gram per kilogram increase in CLA concentration; P < 0.001) with increasing dietary CLA. The carcass lean tissue deposition response to dietary CLA was quadratic in nature and was maximized (+25%) at 5.0 g/kg dietary CLA. Overall, dietary CLA increased the gain to feed ratio and lean tissue deposition and decreased fat deposition in finisher pigs.

J Nutr 1999 Nov;129(11):2037-42

Conjugated linoleic acid reduces body fat mass in overweight and obese humans.

Conjugated linoleic acid (CLA) has been shown to reduce body fat mass (BFM) in animals. To investigate the dose-response relationships of conjugated linoleic acid with regard to BFM in humans, a randomized, double-blind study including 60 overweight or obese volunteers (body mass index 25 to 35 kg/m²) was performed. The subjects were divided into five groups receiving placebo (9 g olive oil), 1.7, 3.4, 5.1 or 6.8 g conjugated linoleic acid per day for 12 weeks, respectively. Dual-energy X-ray absorptiometry was used to measure body composition [measurements at week 0 (baseline), six and 12]. Of the 60 subjects, 47 completed the study. Eight subjects withdrew from the study due to adverse events; however, no differences among treatment groups were found regarding adverse events. Repeated-measures analysis showed that a significantly higher reduction in BFM was found in the conjugated linoleic acid groups compared with the placebo group (P = 0.03). The reduction of body fat within the groups was significant for the 3.4 and 6.8 g CLA groups (P = 0.05 and P = 0.02, respectively). No significant differences among the groups were observed in lean body mass, body mass index, blood safety variables or blood lipids. The data suggest that conjugated linoleic acid may reduce BFM in humans and that no additional effect on BFM is achieved with doses > 3.4 g CLA/d.

J Nutr 2000 Dec;130(12):2943-8

Conjugated linoleic acid-enriched butter fat alters mammary gland morphogenesis and reduces cancer risk in rats.

Conjugated linoleic acid (CLA) is a potent cancer preventive agent in animal models. To date, all of the in vivo work with CLA has been done with a commercial free fatty acid preparation containing a mixture of c9, t11-, t10, c12- and c11, t13-isomers, although CLA in food is predominantly (80% to 90%) the c9, t11-isomer present in triacylglycerols. The objective of this study was to determine whether a high CLA butter fat has biological activities similar to those of the mixture of free fatty acid CLA isomers. The following four different endpoints were evaluated in rat mammary gland: 1) digitized image analysis of epithelial mass in mammary whole mount; 2) terminal end bud (TEB) density; 3) proliferative activity of TEB cells as determined by proliferating cell nuclear antigen immunohistochemistry; and 4) mammary cancer prevention bioassay in the methylnitrosourea model. It should be noted that TEB cells are the target cells for mammary chemical carcinogenesis. Feeding butter fat CLA to rats during the time of pubescent mammary gland development reduced mammary epithelial mass by 22%, decreased the size of the TEB population by 30%, suppressed the proliferation of TEB cells by 30% and inhibited mammary tumor yield by 53% (P < 0.05). Furthermore, all of the above variables responded with the same magnitude of change to both butter fat CLA and the mixture of CLA isomers at the level of CLA (0.8%) present in the diet. Interestingly, there appeared to be some selectivity in the uptake or incorporation of c9, t11-CLA over t10, c12-CLA in the tissues of rats given the mixture of CLA isomers. Rats consuming the CLA-enriched butter fat also consistently accumulated more total CLA in the mammary gland and other tissues (four- to six-fold increases) compared with those consuming free fatty acid CLA (three-fold increases) at the same dietary level of intake. We hypothesize that the availability of vaccenic acid (t11-18:1) in butter fat may serve as the precursor for the endogenous synthesis of CLA via the Delta9-desaturase reaction. Further studies will be conducted to investigate other attributes of this novel dairy product.

J Nutr 1999 Dec;129(12):2135-42

Carnitine/DHEA

Dehydroepiandrosterone alters Zucker rat soleus and cardiac muscle lipid profiles.

High levels of serum free fatty acids (FFA) and lower proportions of polyunsaturated (PU) FAs, specifically arachidonic acid (AA), are common in obesity, insulin resistance (IR), and type 2 diabetes mellitus. Dehydroepiandrosterone (DHEA) decreases body fat content, dietary fat consumption and insulin levels in obese Zucker rats (ZR), a genetic model of human youth onset obesity and type 2 diabetes. This study was conducted to investigate DHEA's effects on lean and obese ZR serum FFA levels and total lipid (TL) FA profiles in heart and soleus muscle. We postulated that DHEA alters serum FFA levels and tissue TL FA profiles of obese ZR so that they resemble the levels and profiles of lean ZR. If so, DHEA may directly or indirectly alter tissue lipids, FFA flux, and perhaps lower IR in obese ZR. Lean and obese male ZR were divided into six groups with 10 animals in each: obese ad libitum control, obese pair-fed, obese DHEA, lean ad libitum control, lean pair-fed, and lean DHEA. All animals had ad libitum access to a diet whose calories were 50% fat, 30% carbohydrate and 20% protein. Only the diets of the DHEA treatment groups were supplemented with 0.6% DHEA. Pair-fed groups were given the average number of calories per day consumed by their corresponding DHEA group, and ad libitum groups had 24-h access to the DHEA-free diet. Serum FFA levels and heart and soleus TL FA profiles were measured. Serum FFA levels were higher in obese (approximately 1 mmol/L) compared to lean (approximately 0.6 mmol/L) ZR, regardless of group. In hearts, monounsaturated (MU) FA were greater and PU FA were proportionally lower in obese compared to the lean rats. In soleus, saturated and MU FA were greater and PU FA were proportionally lower in the obese compared to the lean rats. DHEA groups displayed significantly increased proportions of TL AA and decreased oleic acid in both muscle types. Mechanisms by which DHEA alters TL FA profiles are a reflection of changes occurring within specific lipid fractions such as FFA, phospholipid, and triglyceride. This study provides initial insights into DHEA's lipid altering effects.

Exp Biol Med (Maywood) 2001 Sep;226(8):782-9

Dehydroepiandrosterone alters phospholipid profiles in Zucker rat muscle tissue.

Insulin-resistant muscle tissue contains low proportions of arachidonic acid (AA), and increased proportions of muscle AA correlate with improved insulin sensitivity. Dehydroepiandrosterone (DHEA) and AA, like the thiazolidinedione drugs that decrease insulin resistance (IR), are peroxisome proliferators. Long-chain fatty acids (FA) have been named the "one true" endogenous ligand for activating the peroxisome proliferator-activator receptor (PPAR), and DHEA has been named a "good candidate" as a naturally occurring indirect activator of PPAR. This study was conducted to determine DHEA's effects on lipid profiles of skeletal and cardiac muscle in lean and obese Zucker rats (ZR), a model of IR, type 2 diabetes mellitus, and obesity. We hypothesize that DHEA may alter long-chain FA profiles in muscle tissue of obese rats such that they more closely resemble that of the lean. In our experiments, we employed a DHEA and a pair-fed (PF) group (n = 6) for 12 lean and 12 obese ZR. For 30 d, the diet of the two DHEA groups was supplemented with 0.6% DHEA; PF groups were given the average daily calories consumed by their corresponding treatment group. Hearts and gastrocnemius muscles were assayed for phospholipid (PL), free FA, and triglyceride (TG) FA profiles. The proportion of PL AA was significantly greater in both muscle types of lean compared to obese rats. Hearts from both DHEA groups had greater PL proportions of AA and less oleic (18:1) acid than their PF controls. Likewise, 18:1 proportions were significantly lower in the gastrocnemius; however, AA proportions were not significantly different. Similar phenotypic profile differences were observed in the TG fraction of both muscle types. There were no DHEA-related TG FA profile alterations.

Lipids 2001 Dec;36(12):1383-6

Continued on Page 3 of 4

[Back to the Magazine Forum](#)

ABSTRACTS

Dietary L-carnitine supplementation in obese cats alters carnitine metabolism and decreases ketosis during fasting and induced hepatic lipidosis.

This study was designed to determine whether dietary carnitine supplement could protect cats from ketosis and improve carnitine and lipid metabolism in experimental feline hepatic lipidosis (FHL). Lean spayed queens received a diet containing 40 (CL group, n = 7) or 1000 (CH group, n = 4) mg/kg of L-carnitine during obesity development. Plasma fatty acid, beta-hydroxybutyrate and carnitine, and liver and muscle carnitine concentrations were measured during experimental induction of FHL and after treatment. In control cats (CL group), fasting and FHL increased the plasma concentrations of fatty acids two- to three-fold ($P < 0.0001$) and beta-hydroxybutyrate > 10-fold (from a basal 0.22 ± 0.03 to 1.70 ± 0.73 after three-week fasting and 3.13 ± 0.49 mmol/L during FHL). In carnitine-supplemented cats, these variables increased significantly ($P < 0.0001$) only during FHL (beta-hydroxybutyrate, 1.42 ± 0.17 mmol/L). L-Carnitine supplementation significantly increased plasma, muscle and liver carnitine concentrations. Liver carnitine concentration increased dramatically from the obese state to FHL in nonsupplemented cats, but not in supplemented cats, which suggests de novo synthesis of carnitine from endogenous amino acids in control cats and reversible storage in supplemented cats. These results demonstrate the protective effect of a dietary L-carnitine supplement against fasting ketosis during obesity induction. Increasing the L-carnitine level of diets in cats with low energy requirements, such as after neutering, and a high risk of obesity could therefore be recommended.

J Nutr 2002 Feb;132(2):204-10

Regulation of carnitine acyltransferase synthesis in lean and obese Zucker rats by dehydroepiandrosterone and clofibrate.

The effects of dehydroepiandrosterone (DHEA) and clofibrate on mitochondrial and peroxisomal proliferation and carnitine acyltransferases [mitochondrial carnitine palmitoyltransferase (CPT) and peroxisomal carnitine octanoyltransferase (COT)] were measured in lean and obese female Zucker rats. DHEA increased total hepatic mitochondrial protein two-fold; clofibrate increased total hepatic peroxisomal protein more than five-fold. Both DHEA and clofibrate administration increased enzyme activities, immunoreactive protein, messenger RNA levels and transcription rates for the carnitine acyltransferases. Transcription rates and messenger RNA concentration for both carnitine acyltransferases correlated with the increases in activity. These data suggest that the hepatic CPT and COT in female Zucker rats are regulated primarily at the transcriptional level by DHEA and clofibrate.

J Nutr 1991 Apr;121(4):525-31

The clinical and metabolic effects of rapid weight loss in obese pet cats and the influence of supplemental oral L-carnitine.

The efficacy, safety, and metabolic consequences of rapid weight loss in privately owned obese cats by means of a canned weight-reduction diet and the influence of orally administered L-carnitine on rate of weight loss, routine clinical evaluations, hepatic ultrasonography, plasma amino acid profiles, and carnitine analytes were evaluated. A double-blinded placebo-controlled design was used with cats randomly divided into 2 groups: Group 1 (n = 14) received L-carnitine (250 mg PO q24h) in aqueous solution and group 2 (n = 10) received an identical-appearing water placebo. Median obesity (body condition scores and percentage ideal body weight) in each group was 25%. Caloric intake was restricted to 60% of maintenance energy requirements (60 kcal/kg) for targeted ideal weight. The reducing formula was readily accepted by all cats. Significant weight loss was achieved by week 18 in each group without adverse effects (group 1 = 23.7%, group 2 = 19.6%). Cats receiving carnitine lost weight at a significantly faster rate ($P < .05$). Significant increases in carnitine values developed in each group ($P < .02$). However, significantly higher concentrations of all carnitine moieties and a greater percentage of acetylcarnitine developed in cats of group 1 ($P < .01$). The dietary formula and described reducing strategy can safely achieve a 20% weight reduction within 18 weeks in obese cats. An aqueous solution of L-carnitine (250 mg PO q12h) was at least partially absorbed, was nontoxic, and significantly increased plasma carnitine analyte concentrations as well as rate of weight loss.

J Vet Intern Med 2000 Nov-Dec;14(6):598-608

Effect of dehydroepiandrosterone sulfate on carnitine acetyl transferase activity and L-carnitine levels in oophorectomized rats.

Alteration in energy metabolism of postmenopausal women might be related to the reduction of dehydroepiandrosterone sulfate (DHEAS). DHEA and DHEAS decline with age, leveling at their nadir near menopause. DHEA and DHEAS modulate fatty acid metabolism by regulating carnitine acyltransferases and CoA. The purpose of this study was to determine whether dietary supplementation with DHEAS would also increase tissue L-carnitine levels, carnitine acetyltransferase (CAT) activity and mitochondrial respiration in oophorectomized rats. Plasma L-carnitine levels rose following oophorectomy in all groups ($P < 0.0001$).

Supplementation with DHEAS was not associated with further elevation of plasma L-carnitine levels, but with increased hepatic total and free L-carnitine ($P = 0.021$ and $P < 0.0001$, respectively) and cardiac total L-carnitine concentrations ($P = 0.045$). In addition, DHEAS supplementation increased both hepatic and cardiac CAT activities ($P < 0.0001$ and $P = 0.05$ respectively). CAT activity positively correlated with the total and free carnitine levels in both liver and heart ($r = 0.764$, $r = 0.785$ and $r = 0.700$, $r = 0.519$, respectively). Liver mitochondrial respiratory control ratio, ADP:O ratio and oxygen uptake were similar in both control and supplemented groups. These results demonstrate that in oophorectomized rats, dietary DHEAS supplementation increases the liver and heart L-carnitine levels and CAT activities. In conclusion, DHEAS may modulate L-carnitine level and CAT activity in estrogen deficient rats. The potential role of DHEAS in the regulation of fatty acid oxidation in postmenopausal women is worthy of investigation.

Biochim Biophys Acta 1997 Feb 18;1344(3):201-9

Carnitine and dehydroepiandrosterone sulfate induce protein synthesis in porcine primary osteoblast-like cells.

Age-related bone loss eventually leads to osteopenia in men and women. The etiology of age-related bone loss is currently unknown; however, decreased osteoblast activity contributes to this phenomenon. In turn, osteoblast proliferation and function is dependent on energy production, thus the loss of energy production that occurs with age may account for the deficient osteoblast activity. Carnitine and dehydroepiandrosterone-sulfate (DHEAS), both of which decline with age, promote energy production through fatty acid metabolism. Thus, we hypothesized that carnitine and DHEAS would increase osteoblast activity in vitro. Accordingly, we measured the effect of carnitine and DHEAS on palmitic acid oxidation as a measure of energy production, and alkaline phosphatase (ALP) activity and collagen type I (COL) as indices of osteoblast function in primary porcine osteoblast-like cell cultures. Carnitine ($10(-3)$ and $10(-1)$ M) but not DHEAS ($10(-9)$, $10(-8)$, and $10(-7)$ M) increased carnitine levels within the cells. Carnitine alone and in combination with DHEAS increased palmitic acid oxidation. Both carnitine and DHEAS alone and in an additive fashion increased ALP activity and COL levels. These results demonstrate that in osteoblast-like cells in vitro, energy production can be increased by carnitine and osteoblast protein production can be increased by both carnitine and DHEAS. These data suggest that carnitine and DHEAS supplementation in the elderly may stimulate osteoblast activity and decrease age-related bone loss.

Calcif Tissue Int 1999 Jun;64(6):527-33

Correlation of serum L-carnitine and dehydro-epiandrosterone sulphate levels with age and sex in healthy adults.

OBJECTIVES: L-carnitine and dehydroepiandrosterone (DHEA) independently promote mitochondrial energy metabolism. We therefore wondered if an age-related deficiency of L-carnitine or DHEA may account for the declining energy metabolism associated with age. **METHODS:** we evaluated serum levels of L-carnitine and the sulphated derivative of DHEA (DHEAS) in a cross-sectional study of 216 healthy adults, aged 20 to 95. **RESULTS:** serum DHEAS levels declined, while total carnitine levels increased with age ($P < 0.0001$). Total and free carnitine and DHEAS levels were lower in women than men ($P < 0.0001$). Esterified/free (E/F) carnitine (inversely related to carnitine availability) increased with age in both sexes ($P=0.012$). **CONCLUSION:** reduced carnitine availability correlates with the age-related decline of DHEAS levels. These results are consistent with the hypothesis that decreased energy metabolism with age relates to DHEAS levels and carnitine availability.

Age Ageing 1999 Mar;28(2):211-6

Therapeutic effects of dehydroepiandrosterone (DHEA) in diabetic mice.

Dehydroepiandrosterone (DHEA), a major adrenal secretory steroid in humans, was therapeutic when fed in a concentration of 0.4% to C57BL/KsJ mice with either non-insulin-dependent or insulin-dependent diabetes. Genetically diabetic (db/db) mice of both sexes develop obesity and a glucose intolerance and hyperglycemia associated with insulin resistance by 2 mo of age, and exhibit beta-cell necrosis and islet atrophy by 4 mo. In contrast, DHEA feeding initiated between 1 and 4 mo of age, while only moderately effective in preventing obesity, did prevent the other pathogenic changes and effected a rapid remission of hyperglycemia, a preservation of beta-cell structure and function, and an increased insulin sensitivity as measured by glucose tolerance tests. DHEA feeding was also therapeutic to normal C57BL/KsJ male mice made diabetic by multiple low doses of streptozotocin (SZ). While DHEA treatments did not block either the direct cytotoxic action of SZ on beta-cells or the development of insulinitis, the steroid significantly moderated the severity of the ensuing diabetes (reduced hyperglycemia and water consumption, and increased plasma insulin and numbers of residual, granulated beta-cells).

Diabetes 1982 Sep;31(9):830-3

Molecular Differences Caused by Differentiation of 3T3-L1 Preadipocytes in the Presence of either Dehydroepiandrosterone (DHEA) or 7-Oxo-DHEA.

The effects of dehydroepiandrosterone (DHEA) and 7-oxo-DHEA on the cell size, adiposity, and fatty acid composition of

differentiating 3T3-L1 preadipocyte cells are correlated with stearoyl-CoA desaturase (SCD) expression (mRNA and protein levels) and enzyme activity. Fluorescence-activated cell sorting shows that preadipocyte cells treated with methylisobutylxanthine, dexamethasone, and insulin (MDI) plus DHEA comprise a population distribution of predominantly large cells with reduced adiposity. In contrast, cells treated with MDI plus 7-oxo-DHEA comprise a population distribution of almost equal proportions of small and large cells that have an adiposity equivalent to cells differentiated with MDI alone. The cells treated with MDI plus DHEA have significantly reduced levels of total fatty acid, mainly due to a dramatic reduction in the level of palmitoleic (Delta(9)-16:1) acid. The cells treated with MDI plus 7-oxo-DHEA have a significantly increased level of total fat, primarily due to increased levels of Delta(9)-16:1 and palmitic (16:0) acids. At the molecular level, the DHEA-treated cells contain lowered amounts of SCD1 mRNA and antibody-detectable desaturase protein, while 7-oxo-DHEA-treated cells contained elevated levels of SCD1 mRNA and protein. Inhibition of differentiation in DHEA-treated cells was also suggested by a reduction in the mRNA level of the adipogenic gene aP2. At the level of microsomal enzymatic activity, SCD activity was decreased in DHEA-treated cells while the SCD activity was increased in 7-oxo-DHEA-treated cells. The changes in mRNA levels and enzyme activity were concentration-dependent and appeared as early as day 3 of the differentiation protocol. The results show that DHEA and 7-oxo-DHEA have distinct modes of action with respect to the complex transcriptional cascade required for differentiation. Furthermore, differences in the insulin-stimulated uptake of 2-deoxyglucose and in the activity of carnitine palmitoyl transferase observed from either DHEA- or 7-oxo-DHEA-treated cells support the ability of DHEA to produce a thermogenic effect in differentiating preadipocytes, while 7-oxo-DHEA promotes differentiation without other changes typical of thermogenesis.

Biochemistry 2002 Apr 30;41(17):5473-82

Characteristics of dehydroepiandrosterone as a peroxisome proliferator.

Treatment of rats with dehydroepiandrosterone (300 mg/kg body weight, per os, 14 days) caused a remarkable increase in the number of peroxisomes and peroxisomal beta-oxidation activity in the liver. The activities of carnitine acetyltransferase, microsomal laurate 12-hydroxylation, cytosolic palmitoyl-CoA hydrolase, malic enzyme and some other enzymes were also increased. The increases in these enzyme activities were all greater in male rats than in female rats. Immunoblot analysis revealed remarkable induction of acyl-CoA oxidase and enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase bifunctional enzyme in the liver and to a smaller extent in the kidney, whereas no significant induction of these enzymes was found in the heart. The increase in the hepatic peroxisomal beta-oxidation activity reached a maximal level at day five of the treatment of dehydroepiandrosterone and the increased activity rapidly returned to the normal level on discontinuation of the treatment. The increase in the activity was also dose-dependent, which was saturable at a dose of more than 200 mg/kg body weight. All these features in enzyme induction caused by dehydroepiandrosterone correlate well with those observed in the treatment of clofibrilic acid, a peroxisome proliferator. Co-treatment of dehydroepiandrosterone and clofibrilic acid showed no synergism in the enhancement of peroxisomal beta-oxidation activity, suggesting the involvement of a common process in the mechanism by which these compounds induce the enzymes. These results indicate that dehydroepiandrosterone is a typical peroxisome proliferator. Since dehydroepiandrosterone is a naturally occurring C19 steroid in mammals, the structure of which is novel compared with those of peroxisome proliferators known so far, this compound could provide particular information in the understanding of the mechanisms underlying the induction of peroxisome proliferation.

Biochim Biophys Acta 1991 Apr 17;1092(2):233-43

Continued on Page 4 of 4

[Back to the Magazine Forum](#)

ABSTRACTS

DHEA/Testosterone

Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study.

A cross-sectional population-based study examined the association between endogenous sex hormones and depressed mood in community-dwelling older men. Participants included 856 men, ages 50 to 89 yr, who attended a clinic visit between 1984 to 1987. Total and bioavailable testosterone, total and bioavailable estradiol, and dihydrotestosterone levels were measured by radioimmunoassay in an endocrinology research laboratory. Depressed mood was assessed with the Beck Depression Inventory (BDI). Levels of bioavailable testosterone and bioavailable estradiol decreased with age, but total testosterone, dihydrotestosterone, and total estradiol did not. BDI scores increased with age. Low bioavailable testosterone levels and high BDI scores were associated with weight loss and lack of physical activity, but not with cigarette smoking or alcohol intake. By linear regression or quartile analysis the BDI score was significantly and inversely associated with bioavailable testosterone (both P s = 0.007), independent of age, weight change, and physical activity; similar associations were seen for dihydrotestosterone (P = 0.048 and P = 0.09, respectively). Bioavailable testosterone levels were 17% lower for the 25 men with categorically defined depression than levels observed in all other men (P = 0.01). Neither total nor bioavailable estradiol was associated with depressed mood. These results suggest that testosterone treatment might improve depressed mood in older men who have low levels of bioavailable testosterone. A clinical trial is necessary to test this hypothesis.

J Clin Endocrinol Metab 1999 Feb;84(2):573-7

Dehydroepiandrosterone replacement in aging humans.

Because so much medical and media attention has been drawn to the alleged benefits of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), it is important to evaluate the effects of replacement therapy objectively using double blind, cross-over, randomized research methodology. In this nine-month study, healthy older men (n = 39) received replacement dose DHEA. Lean body mass, blood hematology, chemistry and endocrine values, as well as urological and psychological data were measured. Data showed some mild and temporary, but significant, changes during oral use of 100 mg DHEA for three months compared with placebo taken for three months. Body composition did not change during the six months of treatment, nor did any urological parameters. Concomitant with the endocrine changes, some small but, significant, variations in blood values (blood urea nitrogen, creatinine, uric acid, alanine transaminase, cholesterol, high density lipoprotein, and potassium) were found. After cessation of DHEA and placebo, followed by three months of no treatment, all values previously found to be altered returned to entry baseline. Well publicized effects of the drug reported by others, such as a sense of well-being or improved sexual function, were not found in this study.

J Clin Endocrinol Metab 1999 May;84(5):1527-33

Serum dehydroepiandrosterone sulfate, testosterone, and biochemical markers of bone turnover in elderly Thai men.

The most abundant human steroid, dehydroepiandrosterone sulfate (DHEAS), may have a multitude of beneficial effects, but declines with age. It is unclear whether DHEAS deficiency is an important factor contributing to increased bone resorption and impaired bone formation that leads to their bone loss or not. Thus, we investigated serum DHEAS, testosterone, osteocalcin (N-MID osteocalcin) and C-terminal telopeptides (beta-CrossLaps) in 121 healthy Thai males without bone diseases. Thirty-nine males (mean age 31.5 +/- 8.2, range 23 to 42 years) were recruited as the normal adult group and 82 males (mean age 61.2 +/- 7.0, range 52 to 77 years) were assigned as the elderly group. DHEAS levels were higher in the adult group compared with the elderly subjects (296.8 +/- 93.4 vs 172.6 +/- 99.8 microg/dL, p < 0.0001). Serum osteocalcin concentrations were also higher in the adult group compared with the elderly males (27.9 +/- 11.1 vs 23.2 +/- 7.9 ng/ml, p = 0.0091). However, serum testosterone and C-terminal telopeptides levels were not significantly different between the two groups. We concluded that low DHEAS concentrations are commonly encountered in elderly males and may relate to low osteocalcin levels due to the osteoblast stimulation effects of DHEAS. These findings may be implicated in the treatment of osteoporosis in elderly men by using DHEAS.

J Med Assoc Thai 2001 Oct;84 Suppl 2:S570-5

Testosterone and dehydroepiandrosterone deficiency, general adiposity and visceral obesity during normal male aging.

Both clinical observations and in vitro studies reveal that sex steroids are essential factors affecting body fat accumulation and distribution of healthy men. An excessive adiposity and visceral obesity are frequently accompanied by an adrenal and gonadal

andropenia among men aged 50 and over. The relationships between an age-related increase in BMI and WHR values and an altered androgen-estrogen activity in the course of normal male aging have not been firmly established, as not all studies have thus far produced consistent results. The effects of androgen substitutive therapy (testosterone and dehydroepiandrosterone) in elderly men suggest the possible relationship between androgens and male visceral adiposity; unfortunately the results of available studies on that issue are also not consistent. Therefore, there is an urgent need to comprehensively establish the androgen contribution in the pathogenesis of male visceral obesity.

Pol Merkuriusz Lek 2001 Aug;11(62):187-90

Testosterone, dehydroepiandrosterone, insulin-like growth factor 1, and insulin in sedentary and physically trained aged men.

The influence of physical activity on dehydroepiandrosterone sulfate (DHEAS), total and free testosterone (TT and FT, respectively), insulin-like growth factor I (IGF-1), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and insulin concentrations in aging men was investigated. Eight trained and nine sedentary men aged 60 to 65 years volunteered to participate in this study. Physical activity was determined during an effort test and evaluated by the measure of the maximal aerobic power ($W(aer,max)$). In the trained aging men, the $W(aer,max)$ was higher than in the sedentary group of matching age [mean (SD) 206.8 (17.1) W versus 136.6 (12.3) W; $P < 0.0001$]. The fat percentage was higher in the sedentary ($n = 9$) than in the trained ($n = 8$) group [23.9 (3.2)% versus 14.6 (3.7)%; $P < 0.0001$]. DHEAS and IGF-1 levels were higher in trained than in sedentary subjects, respectively 2.04 (1) micromol/l versus 1.01 (0.68) micromol/l ($P = 0.02$) and 192.1 (40.1) ng/ml versus 132.8 (31.2) ng/ml ($P = 0.003$). Insulin levels were higher in sedentary subjects [11.2 (3.5) mIU/l versus 7.6 (2.2) mIU/l, $P = 0.03$]. No statistical difference was observed between both groups for FT and total TT values, FSH values and LH values. IGF-1 was correlated with $W(aer,max)$ ($r = 0.64$, $P = 0.003$), and DHEAS was correlated with IGF-1 ($r = 0.59$, $P = 0.01$). We observed a relationship between fat percentage and each of the following hormones: IGF-1 ($r = -0.50$, $P = 0.03$), FT ($r = -0.66$, $P = 0.002$), TT ($r = -0.54$, $P = 0.02$) and insulin ($r = -0.63$, $P = 0.004$). Insulin was inversely correlated with FT ($r = -0.66$, $P = 0.002$) and TT ($r = -0.47$, $P = 0.05$). These results suggest that regular physical activity could maintain higher DHEAS and IGF-1 and lean body mass levels in elderly men, and participate in general well being in older age.

Eur J Appl Physiol 2001 Jul;85(1-2):177-84

Effects of transdermal application of 7-oxo-DHEA on the levels of steroid hormones, gonadotropins and lipids in healthy men.

The aim of this study was to investigate the effect of 7-oxo-DHEA (dehydroepiandrosterone) on the serum levels of steroid sexual hormones, gonadotropins, lipids and lipoproteins in men. 7-oxo-DHEA was applied onto the skin as a gel to 10 volunteers aged 27 to 72 years for five consecutive days. The single dose contained 25 mg 7-oxo-DHEA. Serum concentrations of testosterone, estradiol, cortisol, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), total cholesterol, HDL- and LDL-cholesterol, triglycerides, apolipoprotein A-I and B and lipoprotein(a) were measured before the beginning and shortly after the end of the steroid application. After the treatment, we noted the following significant changes: a decline of testosterone and estradiol levels, increase of LH, HDL-cholesterol and apolipoprotein A-I levels. The decrease of total cholesterol levels was of the borderline significance. A slight but significant increase was found in apolipoprotein B and lipoprotein (a). The most expressive was the fall of the atherogenic index. We suggest that the gel containing 7-oxo-DHEA might be a suitable drug for improving the composition of the steroid and lipid parameters in elderly men.

Physiol Res 2001;50(1):9-18

Effects of DHEA replacement on bone mineral density and body composition in elderly women and men.

OBJECTIVE: Dehydroepiandrosterone (DHEA) is a precursor for both oestrogens and androgens. Its marked decline with ageing may influence age-related changes in tissues influenced by sex hormones. The aim of this study was to determine the effects of DHEA replacement on bone mineral density (BMD) and body composition in elderly women and men with low serum DHEA sulphate (DHEAS) levels. **DESIGN:** Prospective six month trial of oral DHEA replacement, 50 mg/day. **PATIENTS:** Experimental subjects were 10 women and eight men, aged 73 +/- 1 years. Control subjects were 10 women and eight men, aged 74 +/- 1 years. **MEASUREMENTS:** BMD, body composition, serum markers of bone turnover, serum lipids and lipoproteins, oral glucose tolerance, serum IGF-I, total serum oestrogens and testosterone. **RESULTS:** BMD of the total body and lumbar spine increased (mean +/- SEM; 1.6 +/- 0.6% and 2.5 +/- 0.8%, respectively; both $P < \text{or} = 0.05$), fat mass decreased (- 1.3 +/- 0.4 kg; $P < 0.01$) and fat-free mass increased (0.9 +/- 0.4 kg; $P < \text{or} = 0.05$) in response to DHEA replacement. DHEA replacement also resulted in increases in serum IGF-I (from 108 +/- 8 to 143 +/- 7 microg/l; $P < 0.01$) and total serum testosterone concentrations (from 10.7 +/- 1.2 to 15.6 +/- 1.8 nmol/l in the men and from 2.1 +/- 0.2 to 4.5 +/- 0.4 nmol/l in the women; both $P < \text{or} = 0.05$). **CONCLUSIONS:** The results provide preliminary evidence that DHEA replacement in those elderly women and men who have very low serum DHEAS levels can partially reverse age-related changes in fat mass, fat-free mass, and BMD, and raise the possibility that increases in IGF-I and/or testosterone play a role in mediating these effects of DHEA.

Clin Endocrinol (Oxf) 2000 Nov;53(5):561-8

The acute effect of dexamethasone on plasma leptin concentrations and the relationships between fasting leptin, the IGF-I/IGFBP system, dehydroepiandrosterone, androstenedione and testosterone in an elderly population.

OBJECTIVE: To investigate the acute effect of dexamethasone administration on serum leptin levels and the relationships between dehydroepiandrosterone (DHEAS), androstenedione, testosterone and the IGF-I/IGFBP system and leptin levels in healthy elderly humans. **METHODS:** In 209 healthy elderly individuals (95 men, 114 women, aged 55 to 80 years) measurements were made in the fasting state (0800 h) and after an overnight dexamethasone suppression test (1 mg p.o. at 2300 h. **RESULTS:** Mean leptin levels increased from 6.2 +/- 0.4 (SE) micrograms/l to 7.3 +/- 0.5 (SE) micrograms/l in men and from 18.9 +/- 1.4 (SE) micrograms/l to 23.9 +/- 1.8 (SE) micrograms/l in women after 1 mg dexamethasone overnight ('post treatment')(P < 0.001 for both sexes). There was a significant relationship between post-treatment leptin and dexamethasone levels (men: P = 0.002; women: P < 0.001). The increase in leptin levels after dexamethasone administration was only partially related to the increase in plasma insulin concentrations. Cortisol levels were not related to leptin. In multivariate analyses the relationship between post-treatment leptin and dexamethasone levels remained after adjustment for post-treatment insulin levels, BMI, waist:hip ratio (WHR) and age (men: P < 0.001; women: P = 0.001). Plasma (free and total) IGF-I and IGFBP-3 levels were not related to leptin levels in men or women. IGFBP-1 levels were inversely related to leptin levels (P = 0.02), but this relationship was lost after adjustment for insulin, and/or BMI. In multivariate analyses the relationship between leptin and DHEAS was inverse in women (P = 0.04) (after adjustment for BMI, WHR, insulin and glucose), while there was no relationship between leptin and DHEAS in men. **CONCLUSIONS:** Administration of dexamethasone acutely increased leptin levels within 9 h in this elderly population. This increase was only partly related to changes in circulating insulin concentrations, but was independent of BMI and waist:hip ratio. No relation existed between leptin and (free or total) IGF-I and IGFBP-3 in men or women. Dehydroepiandrosterone was inversely related to leptin in women. These findings suggest a contributory regulatory role for corticosteroids in modulating circulating leptin concentrations in elderly healthy individuals of both sexes, which is at least in part independent of insulin, BMI and waist:hip ratio. Dehydroepiandrosterone might play a role in the gender-specific differences in serum leptin levels.

Clin Endocrinol (Oxf) 1998 May;48(5):621-6

Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue.

The secretion and the blood levels of the adrenal steroid dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) decrease profoundly with age, and the question is posed whether administration of the steroid to compensate for the decline counteracts defects associated with aging. The commercial availability of DHEA outside the regular pharmaceutical-medical network in the United States creates a real public health problem that may be resolved only by appropriate long-term clinical trials in elderly men and women. Two hundred and eighty healthy individuals (women and men 60 to 79 years old) were given DHEA, 50 mg, or placebo, orally, daily for a year in a double-blind, placebo-controlled study. No potentially harmful accumulation of DHEAS and active steroids was recorded. Besides the reestablishment of a "young" concentration of DHEAS, a small increase of testosterone and estradiol was noted, particularly in women, and may be involved in the significantly demonstrated physiological-clinical manifestations here reported. Bone turnover improved selectively in women > 70 years old, as assessed by the dual-energy x-ray absorptiometry (DEXA) technique and the decrease of osteoclastic activity. A significant increase in most libido parameters was also found in these older women. Improvement of the skin status was observed, particularly in women, in terms of hydration, epidermal thickness, sebum production, and pigmentation. A number of biological indices confirmed the lack of harmful consequences of this 50 mg/day DHEA administration over one year, also indicating that this kind of replacement therapy normalized some effects of aging, but does not create "supermen/women" (doping).

Proc Natl Acad Sci U S A 2000 Apr 11;97(8):42784

Relationship between serum dehydroepiandrosterone sulfate, androstenedione and sex hormones in men and women.

Previous reports of a correlation between serum dehydroepiandrosterone sulfate (DHEAS) and testosterone in both men and women have led to the suggestion that adrenal and gonadal secretion are related. In the present study, the correlation of DHEAS with testosterone and free testosterone (FT) in both normal men and women was tested. Androstenedione, estradiol, sex hormone binding globulin (SHBG), and insulin were also measured and their correlations determined. All correlations were controlled for age and body mass index. In the men in the study, DHEAS did not correlate with testosterone or FT but correlated strongly with androstenedione. In the women, DHEAS correlated strongly with testosterone, FT, and androstenedione; androstenedione in turn correlated strongly with testosterone and FT. DHEAS showed no correlations with estradiol, SHBG, or insulin in the men or women. The lack of a correlation between DHEAS and testosterone in normal men is consistent with the independent secretion of these hormones by the adrenal and testis, respectively. The finding of a strong DHEAS-testosterone correlation in normal women may be explained by parallel adrenal secretion in response to trophic stimuli, i.e., without invoking an adrenal-gonadal interaction

Eur J Endocrinol 1996 Feb;134(2):201-6

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any 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.