

Lupus

ABSTRACTS

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The type of dietary fat affects the severity of autoimmune disease in NZB/NZW mice.

Alexander NJ, Smythe NL, Jokinen MP

Am J Pathol 1987 Apr;127(1):106-21

The type of dietary fat dramatically affects the onset of autoimmune disease in lupus-prone female New Zealand Black/New Zealand White F1 (B/W) mice. Disease development was strikingly slowed in mice fed a diet containing quantities of omega-3 fatty acids (fish oil, FO). By 10 months of age, 94% of the FO mice were still living, whereas all the mice fed a saturated fat diet (lard,L) were dead. Those mice fed a corn oil (CO) diet were intermediate with 35% alive at the 10-month time evaluation. Long after the L and CO groups had succumbed to glomerulonephritis, the FO group had negligible proteinuria. Both B and T cell function, particularly antibody production and resultant circulating immune complex (CIC) levels, were modified by the type of dietary fat. FO mice exhibited lower levels of anti-ds-DNA and lower levels of CICs than L or CO mice. B/W antibody response to a T-independent antigen (DNP-dextran) was enhanced at 8 months of age in FO mice, whereas it was suppressed in L mice. T-dependent (sheep red blood cell) responses at that time period were reduced in all the diet groups, a reflection of the reduced numbers of accessory T cells as determined by FACS analysis. The natural killer (NK) response to YAC-1 cells decreased in the L group from 5 to 9 months of age but remained unchanged in the CO and FO groups. Severe glomerulonephritis was the most common histopathologic finding in the L and CO groups. Arteritis was found in the spleens of nearly all the L and CO mice. Arteritis of the heart, colon and intestine, stomach, kidney, and liver were also seen principally in the L mice. In contrast, most FO mice had minimal to mild glomerulonephritis and no or minimal arteritis in the spleen. It is likely omega-3 fatty acids of fish oil reduce immune-complex-induced glomerulonephritis through production of prostaglandin metabolites with attenuated activity and/or through altering cell membrane structure and fluidity, which may, in turn, affect the responsiveness of immune cells.

Cytokine dysregulation and increased oxidation is prevented by dehydroepiandrosterone in mice infected with murine leukemia retrovirus.

Araghi-Niknam M, Zhang Z, Jiang S, Call O, Eskelson CD, Watson RR Arizona Prevention Center, University of Arizona, Tucson 85724, USA.

Proc Soc Exp Biol Med 1997 Dec;216(3):386-91

The effects of murine leukemia retrovirus infection on production of cytokines was investigated in mice fed different doses of dehydroepiandrosterone (DHEA). Young C57BL/6 female mice were injected with LP-BM5 murine retrovirus or were kept as uninfected controls. Two weeks later, each group was divided into subgroups: fed unsupplemented AIN 93 diet as the control, or diets supplemented with 0.02% DHEA (0.9 mg/mouse/day) or 0.06% DHEA (2.7 mg/mouse/day). The uninfected mice supplemented with 0.06% DHEA showed a significant ($P < 0.05$) increase in interleukin-2 (IL-2) and gamma-interferon (IFN-gamma) production, and hepatic vitamin E levels. Retroviral infection induced severe oxidative stress that was reduced by DHEAS supplementation in retrovirally infected mice. DHEA supplementation prevented the retrovirus-induced loss of cytokines (IL-2 and IFN-gamma) secretion by mitogen stimulated spleen cells. DHEA also suppressed the production of cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) by T helper 2 (Th2) cells which were otherwise stimulated by retrovirus infection. Thus, immune dysfunction and increased oxidation induced by murine retrovirus infection were largely prevented by DHEA.

Lupus Clinical Overview 1998.

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Dr. Belmont's Homepage (www.cerebel.com/lupus).

The laughter-immune connection. An interview with J.R. Dunn.

Berk, L., Tan, S.

Humor and Health Letter 1994 Nov-Dec; 3(6): 1-8.

The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders.

Bottiglieri T, Hyland K, Reynolds EH. Metabolic Disease Center, Baylor Research Institute, Dallas, Texas.

Drugs. 1994 Aug;48(2):137-52.

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; SAMe). SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of SAMe is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS SAMe concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. SAMe has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. SAMe has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAMe) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders.

Efficacy of thalidomide in the treatment of refractory ankylosing spondylitis.

Breban M, Gombert B, Amor B, Dougados M Hopital Cochin, Universite Rene Descartes, Paris, France.

Arthritis Rheum 1999 Mar;42(3):580-1

No abstract.

Laboratory tests for rheumatic diseases. When are they useful?

Callegari PE, Williams WV. Division of Rheumatology, University of Pennsylvania School of Medicine, Philadelphia, USA.

Postgrad Med. 1995 Apr;97(4):65-8, 71-4.

Because negative tests often do not exclude a rheumatic disease and positive tests do not always diagnose it, judicious use of laboratory testing in patients with suspected rheumatic disease is essential. The final diagnosis must be made clinically. However, when the tests are used in conjunction with clinical manifestations, they may help differentiate the numerous rheumatic disorders, and they may also be of value in monitoring activity of the disease.

Flaxseed in lupus nephritis: a two-year nonplacebo-controlled crossover study.

Clark WF, Kortas C, Heidenheim AP, Garland J, Spanner E, Parbtani A. London Health Sciences Centre, The University of Western Ontario, Canada. william.clark@lhsc.on.ca

J Am Coll Nutr 2001 Apr;20(2 Suppl):143-8

OBJECTIVE: The objective of this study was to determine the renoprotective effects of ground flaxseed in patients with lupus nephritis.

METHODS: Forty patients with lupus nephritis were asked to participate in a randomized crossover trial of flaxseed. Twenty-three agreed and were randomized to receive 30 grams of ground flaxseed daily or control (no placebo) for one year, followed by a twelve-week washout period and the reverse treatment for one year. At baseline and six month intervals, serum phospholipids, flaxseed sachet counts, serum creatinine, 12-hour urine albumin excretion and urine albumin to creatinine ratios, serum viscosity and plasma lipids were measured.

RESULTS: There were eight drop-outs and of the 15 remaining subjects flaxseed sachet count and serum phospholipid levels indicated only nine were adherent to the flaxseed diet. Plasma lipids and serum viscosity were unaltered by the flaxseed supplementation whereas serum creatinine in the compliant patients during flaxseed administration declined from a mean of 0.97+/-0.31 mg/dL to a mean of 0.94+/-0.30 mg/dL and rose in the control phase to a mean of 1.03+/-0.28 mg/dL [p value <0.08]. Of the fifteen patients who completed the study, similar changes were noted [p value <0.1]. The nine compliant patients had lower serum creatinines at the end of the two-year study than the 17 patients who refused to participate [p<0.05]. Microalbumin at baseline declined in both control and flaxseed time periods, but there was a trend for a greater decline during flaxseed administration [p<0.2].

CONCLUSIONS: Flaxseed appears to be renoprotective in lupus nephritis, but this interpretation is affected by under powering due to poor adherence and potential Hawthorne effects.

Pavlovian conditioning of the immune system.

Int Arch Allergy Immunol 1994 Oct;105(2):101-6

In the classical Pavlovian conditioning paradigm, a stimulus that unconditionally elicits a physiological response is repeatedly paired with a neutral stimulus that does not elicit that same response. Eventually, the neutral stimulus becomes a conditioned stimulus in that it elicits the physiological response in the absence of an unconditioned stimulus. Here we summarize experiments in which Pavlovian conditioning has revealed an intimate relationship between the central nervous system and the immune system.

Dietary intervention in systemic lupus erythematosus: 4 cases of clinical remission and reversal of abnormal pathology.

Cooke, H.M., Reading, C.M.

Int. Clin. Nutr. Rev. 1985; 5(4): 166-76.

No abstract found

The role of diet in animal models of systemic lupus erythematosus: possible implications for human lupus.

Corman LC

Semin Arthritis Rheum 1985 Aug;15(1):61-9

Studies of diet in the mouse model of SLE have established the beneficial effects of a low calorie, low fat diet in these animals as well as the importance of the specific source of dietary fat. The role of zinc in murine and human SLE is less clear. The reported improvement of patients with SLE and other related diseases on a low phenylalanine and tyrosine diet high in fish content, and the lupus inducing capacity of a nonphysiologic amino acid present in alfalfa are also reviewed. The need for carefully controlled prospective studies of diet in patients with SLE is noted, and a diet of potential therapeutic benefit is described.

Thalidomide: Efficacy and Safety in 30 Patients with Lupus and Skin Involvement 2001.

Cuadrado, M.J., Smith, E., Gordon, P. et al.

Presented at the 65th Annual Meeting of the American College of Rheumatology, San Francisco, California, November 10-15, 2001.

Genetics and lupus.

DeHoratius, R.

Learning About Lupus: A User Friendly Guide 1997. Moore, M., McGrory, C., Rosenthal, R., Eds. Ardmore, PA: Lupus Foundation of Delaware Valley.

Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial.

Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, Boumpas DT, Klippel JH, Balow JE, Steinberg AD National Institutes of Health, Bethesda, Maryland, USA.

Ann Intern Med 1996 Oct 1;125(7):549-57

BACKGROUND: Uncertainty exists about the efficacy and toxicity of bolus therapy with methylprednisolone or of the combination of methylprednisolone and cyclophosphamide in the treatment of lupus nephritis.

OBJECTIVE: To determine 1) whether intensive bolus therapy with methylprednisolone is an adequate substitute for bolus therapy with cyclophosphamide and 2) whether the combination of methylprednisolone and cyclophosphamide is superior to bolus therapy with methylprednisolone or cyclophosphamide alone.

DESIGN: Randomized, controlled trial with at least 5 years of follow-up. **SETTING:** Government referral-based research hospital. **PATIENTS:** 82 patients with lupus nephritis who had 10 or more erythrocytes per high-power field, cellular casts, proteinuria (> 1 g

of protein per day), and a renal biopsy specimen that showed proliferative nephritis. INTERVENTIONS: Bolus therapy with methylprednisolone (1 g/m² body surface area), given monthly for at least 1 year; bolus therapy with cyclophosphamide (0.5 to 1.0 g/m² body surface area), given monthly for 6 months and then quarterly; or bolus therapy with both methylprednisolone and cyclophosphamide.

MEASUREMENTS: 1) Renal remission (defined as < 10 dysmorphic erythrocytes per high-power field, the absence of cellular casts, and excretion of < 1 g of protein per day without doubling of the serum creatinine level), 2) prevention of doubling of the serum creatinine level, and 3) prevention of renal failure requiring dialysis.

RESULTS: Renal remission occurred in 17 of 20 patients in the combination therapy group (85%), 13 of 21 patients in the cyclophosphamide group (62%), and 7 of 24 patients in the methylprednisolone group (29%) (P < 0.001). Twenty-eight patients (43%) did not achieve renal remission. By life-table analysis, the likelihood of remission during the study period was greater in the combination therapy group than in the methylprednisolone group (P = 0.028). Combination therapy and cyclophosphamide therapy were not statistically different. Adverse events were amenorrhea (seen in 41% of the cyclophosphamide group, 43% of the combination therapy group, and 7.4% of the methylprednisolone group), cervical dysplasia (seen in 11% of the cyclophosphamide group, 7.1% of the combination therapy group, and 0% of the methylprednisolone group), avascular necrosis (seen in 11% of the cyclophosphamide group, 18% of the combination therapy group, and 22% of the methylprednisolone group), herpes zoster (seen in 15% of the cyclophosphamide group, 21% of the combination therapy group, and 3.7% of the methylprednisolone group) and at least one infection (seen in 26% of the cyclophosphamide group, 32% of the combination therapy group, and 7.4% of the methylprednisolone group).

CONCLUSIONS: Monthly bolus therapy with methylprednisolone was less effective than monthly bolus therapy with cyclophosphamide. A trend toward greater efficacy with combination therapy was seen.

Dehydroepiandrosterone synergizes with antioxidant supplements for immune restoration in old as well as retrovirus-infected mice.

Jiang, S., Lee, J., Zang, Z. et al.

J. Nutr. Biochem. 1998; 9(7): 362-9.

Inhibiting effects of theanine on caffeine stimulation evaluated by EEG in the rat.

Kakuda T, Nozawa A, Unno T, Okamura N, Okai O. Central Research Institute, Itoen Ltd., Shizuoka, Japan. ITN00527@nifty.ne.jp

Biosci Biotechnol Biochem. 2000 Feb;64(2):287-93.

In this study, the inhibiting action of theanine on the excitation by caffeine at the concentration regularly associated with drinking tea was investigated using electroencephalography (EEG) in rats. First, the stimulatory action by caffeine i.v. administration at a level higher than 5 micromol/kg (0.970 mg/kg) b.w. was shown by means of brain wave analysis, and this level was suggested as the minimum dose of caffeine as a stimulant. Next, the stimulatory effects of caffeine were inhibited by an i.v. administration of theanine at a level higher than 5 micromol/kg (0.781 mg/kg) b.w., and the results suggested that theanine has an antagonistic effect on caffeine's stimulatory action at an almost equivalent molar concentration. On the other hand, the excitatory effects were shown in the rat i.v. administered 1 and 2 micromol/kg (0.174 and 0.348 mg/kg) b.w. of theanine alone. These results suggested two effects of theanine, depending on its concentration.

Testosterone inhibits immunoglobulin production by human peripheral blood mononuclear cells.

Kanda N, Tsuchida T, Tamaki K Department of Dermatology, Faculty of Medicine, University of Tokyo, Japan.

Clin Exp Immunol 1996 Nov;106(2):410-5

We studied the in vitro effect of testosterone on spontaneous immunoglobulin production by human peripheral blood mononuclear cells (PBMC). Testosterone inhibited IgG and IgM production by PBMC both from males and females. The inhibitory effect of testosterone was revealed at doses more than 1 nM, increased dose-dependently, and reached a plateau at 100 nM. At doses < 1000 nM, testosterone did not reduce cell viability. Testosterone treatment reduced IgG production by 59.0% and that of IgM by 61.3% compared with control. Immunoglobulin production by B cells was also suppressed by testosterone, though the magnitude of the suppressive effect on B cells was lower than that on whole PBMC; testosterone-induced decrease of IgG production compared with control was 26.9% and that of IgM was 24.9%. Exogenous IL-6 partially restored the impaired immunoglobulin production of testosterone-treated PBMC; IgG production in testosterone culture was increased by IL-6 from 35.6% to 66.5% of control and that of IgM was also increased from 38.9% to 71.2%, respectively. Testosterone treatment reduced IL-6 production of

monocytes by 78.4% compared with control, but neither affected that of T cells or B cells. These results suggest that testosterone may suppress immunoglobulin production of human PBMC directly by inhibiting B cell activity and indirectly by reducing IL-6 production of monocytes. It is thus indicated that this hormone may have protective and therapeutic effects on human autoimmune diseases.

Aberrant hormone balance in fetal autoimmune NZB/W mice following prenatal exposure to testosterone excess or the androgen blocker flutamide.

Keisler LW, vom Saal FS, Keisler DH, Rudeen PK, Walker SE Department of Veterans Affairs Medical Center, Columbia, Missouri.

Biol Reprod 1995 Nov;53(5):1190-7

F1 hybrid New Zealand Black (NZB) x New Zealand White (NZW) (NZB/W) mice are hormone-sensitive models of the human disease systemic lupus erythematosus. In this study, NZB/W fetuses produced by pregnant NZB mice were compared with F1 C57BL/6 x DBA/2 (C57/DBA2) hybrid fetuses produced by nonautoimmune C57BL/6 females. Dams of both strains were treated with testosterone or the androgen blocker flutamide to alter the hormonal environment in late gestation. Hormonal changes in male fetuses carried by treated dams were of interest because hormonal manipulation using either testosterone or flutamide has been shown to increase longevity in male NZB/W offspring. Testosterone-implanted NZB dams developed the expected elevations in circulating maternal testosterone, whereas C57BL/6 dams treated with either testosterone or flutamide had elevated maternal serum testosterone concentrations. The treatment-induced changes in circulating testosterone in NZB dams and C57BL/6 dams were not reflected in serum from 18-day NZB/W or C57/DBA2 fetuses. Male NZB/W offspring from untreated control NZB dams had unexpectedly high levels of serum estradiol and alpha fetoprotein and relatively low extractable testicular testosterone, compared with nonautoimmune male control fetuses. Maternal testosterone treatments produced a significant decrease in serum estradiol in NZB/W male fetuses, and placental testosterone content was also reduced. Our findings suggest that placental androgen control is regulated differently in the autoimmune NZB-NZB/W vs. the nonautoimmune C57BL/6-C57/DBA2 maternal-placental-fetal unit.

A fish oil diet rich in eicosapentaenoic acid reduces cyclooxygenase metabolites, and suppresses lupus in MRL-mice.

Kelly, V. et al.

J. Immunol. 1985 Mar; 134(3): 1914-9.

No abstract available.

Factors associated with low bone mineral density in female patients with systemic lupus erythematosus.

Lakshminarayanan S, Walsh S, Mohanraj M, Rothfield N. Department of Medicine, University of Connecticut Health Center, Farmington 06030-1310, USA.

J Rheumatol 2001 Jan;28(1):102-8

OBJECTIVE: To study risk factors for low bone mineral density (BMD, g/cm) in patients with systemic lupus erythematosus (SLE).

METHODS: Ninety-two consecutive patients with SLE followed by rheumatology faculty between 1997 and 1999 completed a questionnaire regarding lifestyle during the clinic visit, a chart review was performed, and data were collected for the time of the first dual energy x-ray absorptiometry (DXA) examination. Univariate and multivariate statistical analyses were used to assess relationships between various risk factors and BMD.

RESULTS: Ninety-eight percent of patients had received prednisone, 51% were postmenopausal (9 of whom received hormone replacement therapy), 68% had received hydroxychloroquine, and 15% were osteoporotic. The following factors were found to be significantly related to lower BMD by univariate analysis: Caucasian race, older age at diagnosis, higher age at the time of the first DXA, longer disease duration, higher cumulative corticosteroid dose, higher SLE Damage Index score, and postmenopausal status. In the multivariate analysis only the following factors were significant: Caucasian race, increased number of pregnancies, postmenopausal status, higher SLE Damage Index, and higher cumulative corticosteroid dose. An unexpected finding was that taking hydroxychloroquine was the only factor associated with higher BMD of the hip and spine in the univariate analysis, and it remained predictive of higher BMD of the hip and spine in the multivariate analysis.

CONCLUSION: Hydroxychloroquine appears to protect against low BMD in corticosteroid treated patients with SLE.

Diet and lupus.

Leiba A, Amital H, Gershwin ME, Shoenfeld Y. Research Unit of Autoimmune Diseases, Department of Medicine B Chaim Sheba Medical Center, Tel Hashomer, Israel.

Lupus. 2001;10(3):246-8.

The effect of dietary modifications has been extensively studied in lupus animal models. Calorie, protein, and especially fat restriction, caused a significant reduction in immune-complex deposition in the kidney, reduced proteinuria and prolongation of the mice's life span. The addition of polyunsaturated fatty acids (PUFAs), such as fish oil or linseed oil, was also related to decreased mice morbidity and mortality in animal models of lupus and of antiphospholipid syndrome. PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) competitively inhibit arachidonic acid with a resultant decrease in inflammatory eicosanoids and cytokines. Human studies support the effect of a PUFAs-enriched diet, both serologically and clinically. Large scale clinical studies are needed to confirm the primary results.

Lupus: Support and Survival: Vitamins and Nutritional Management of Lupus 1988.

Lupus Alert.

Rockville, MD: Lupus Foundation of America (www.lupus.org).

Systemic lupus erythematosus.

Pisetsky, D.S. Primer on the Rheumatic Diseases, Tenth Edition 1993, pp. 100-5. Schumacher, H.R., Klippel, J.H., Koopman, W.J., Eds. Atlanta: The Arthritis Foundation.

Cytotoxic therapy in systemic lupus erythematosus. Experience from a single center.

Rahman P, Humphrey-Murto S, Gladman DD, Urowitz MB Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Hospital, Ontario, Canada.

Medicine (Baltimore) 1997 Nov;76(6):432-7

The present survey of cytotoxic therapy from a single large lupus clinic has shown that approximately 33% of the patients have received cytotoxic therapy at some point in their course. These agents were initiated for a variety of manifestations, with renal manifestations being the major indication, accounting for 28.2% of the cytotoxic agents used. Other common indications for initiation of cytotoxic therapy included steroid sparing (18.4%), global flare (12.5%), neurologic manifestations (11.4%), and musculoskeletal (8.6%). Azathioprine, methotrexate, and cyclophosphamide accounted for 98% of all cytotoxic agents used. Azathioprine was the most frequently used cytotoxic drug (70%), followed by methotrexate (21.5%) and cyclophosphamide (9.4%). Cytotoxic agents were used sequentially in 12.5% of patients and in combination in 4.2% of the patients. Overall, the use of cytotoxic therapy appears to be beneficial in reducing global disease activity, as the mean SLEDAI fell by 2.59 (33%) over 6 months of cytotoxic therapy, and the mean steroid dose was reduced by 37% over the same time period. There was also an improvement in most organ-specific indications with the use of cytotoxic agents. Overall the cytotoxic agents were well tolerated, with 17% of the courses being discontinued due to a side effect. Cytopenia was the most common side effect necessitating discontinuation of cytotoxic agents.

Estrogen increases CD40 ligand expression in T cells from women with systemic lupus erythematosus.

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J Rheumatol. 2001 Dec;28(12):2644-9.

OBJECTIVE: To examine the in vitro effects of estrogen on CD40 ligand (CD40L) expression in peripheral blood T cells isolated from patients with systemic lupus erythematosus (SLE) and normal controls.

METHODS: T cells from female patients with SLE and controls were cultured in serum-free medium without and with 2-fluoroestradiol. Some T cells were activated by further culture on anti-CD3 coated plates. Calcineurin was activated in some T cells by culture in ionomycin. Cell surface CD40L was quantitated by FACS analysis. mRNA expression was measured using semiquantitative PCR.

RESULTS: Lupus T cells cultured in medium containing 2-fluoroestradiol showed a significant ($p = 0.04$) increase in the amount of

CD40L on the cell surface, but not in the number of positive cells, compared to the same T cells cultured without estradiol. Estradiol did not significantly change CD40L expression on the surface of T cells from normal women. In addition, the difference in cell surface CD40L between T cells cultured without and with estradiol was significantly greater ($p = 0.048$) on SLE than on normal T cells. Culture of SLE T cells in medium containing 2-fluoroestradiol followed by T cell receptor (TCR) activation for 2 h using anti-CD3 resulted in a significant ($p = 0.04$) estrogen dependent increase in CD40L mRNA. The estrogen dependent increases in SLE T cell CD40L mRNA and cell surface protein were blocked by the estrogen receptor antagonist ICI 182,780. SLE and normal T cells pretreated with estradiol and cultured with ionomycin for 2 h to activate calcineurin showed no significant differences in CD40L mRNA.

CONCLUSION: These results suggest that estradiol, working through the estrogen receptor, stimulates the expression of CD40L in unstimulated and activated SLE T cells. Estradiol effects may be exerted on multiple regulatory steps that control CD40L expression. The estrogen dependent increase in CD40L expression could hyperstimulate SLE T cells and thereby contribute to the pathogenesis of SLE.

The protective effect of dietary fish oil on murine lupus.

Robinson DR, Prickett JD, Polisson R, Steinberg AD, Levine L

Prostaglandins 1985 Jul;30(1):51-75

Dietary marine lipids markedly reduce the severity of glomerulonephritis and its associated mortality in inbred strains of mice developing autoimmune disease, a model for human systemic lupus erythematosus. We report here the influence of varying the dose of menhaden oil and the timing of its administration on the mortality of female (NZB x NZW) F1 mice. After ingesting 25 wt% menhaden oil (MO) for periods of 1.5 weeks to 12 months, there was a stable content of tissue n-3 fatty acids, with total n-3 fatty acids of 28% and 35% in spleen and liver, respectively. The extent of protection from mortality was dependent on the dose of MO with marked protection at doses of 11 to 25%, marginal protection at 5.5% and no protection at 2.5% MO. Delay in the institution of MO until ages 5 or 7 months still resulted in large reductions of mortality. Conversely, institution of a MO diet from 6 weeks until ages 5 to 7 months followed by a change to beef tallow resulted in little protection. Serum levels of 4 cyclooxygenase products were reduced ranging from 26 to 76% in mice fed MO diets, compared to mice fed beef tallow, based on radioimmunoassay. The degree of reduction of mortality on different doses of MO was correlated best with tissue levels of C22:5, and levels of C20:5 and C22:6 were similar at high and low doses of MO, suggesting that levels of 22:5 may be related to the protective effects of marine lipids on autoimmune disease.

Plasmapheresis and subsequent pulse cyclophosphamide in severe systemic lupus erythematosus. Preliminary results of the LPSG-Trial.

Schroeder, J.O., Schwab, U., Zeuner, R. et al.

Arthritis Rheum. 1997 Sep; 40(9, Suppl.): S325.

No abstract available.

Successful treatment of lupus erythematosus cystitis with DMSO.

Sotolongo JR Jr, Swerdlow F, Schiff HI, Schapira HE

Urology 1984 Feb;23(2):125-7

Systemic lupus erythematosus patients sometimes present with pathologically confirmed lupus interstitial cystitis. Treatment with prednisone has not been observed to be successful. Two patients are presented who were successfully treated with intravesical dimethyl sulfoxide (DMSO).

Low serum levels of dehydroepiandrosterone may cause deficient IL-2 production by lymphocytes in patients with systemic lupus erythematosus (SLE).

Suzuki T, Suzuki N, Engleman EG, Mizushima Y, Sakane T Department of Immunology, St. Marianna University School of Medicine, Kanagawa, Japan.

Clin Exp Immunol 1995 Feb;99(2):251-5

The principal cause of IL-2 deficiency, a common feature of both murine lupus and human SLE, remains obscure. Recent studies

of our own as well as others have shown that dehydroepiandrosterone (DHEA), an intermediate compound in testosterone synthesis, significantly up-regulates IL-2 production of T cells, and that administration of exogenous DHEA or IL-2 via a vaccinia construct to murine lupus dramatically reverses their clinical autoimmune diseases. Thus, we have examined serum levels of DHEA in patients with SLE to test whether abnormal DHEA activity is associated with IL-2 deficiency of the patients. We found that nearly all of the patients examined have very low levels of serum DHEA. The decreased DHEA levels were not simply a reflection of a long term corticosteroid treatment which may cause adrenal atrophy, since serum samples drawn at the onset of disease, which are devoid of corticosteroid treatment, also contained low levels of DHEA. In addition, exogenous DHEA restored impaired IL-2 production of T cells from patients with SLE in vitro. These results indicate that defects of IL-2 synthesis of patients with SLE are at least in part due to the low DHEA activity in the serum.

Effects of oral administration of type II collagen on rheumatoid arthritis.

Trentham DE, Dynesius-Trentham RA, Orav EJ, Combitchi D, Lorenzo C, Sewell KL, Hafler DA, Weiner HL Department of Medicine, Beth Israel Hospital, Boston, MA. as reported by The Arthritis Foundation (www.arthritis.org).

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Rheumatoid arthritis is an inflammatory synovial disease thought to involve T cells reacting to an antigen within the joint. Type II collagen is the major protein in articular cartilage and is a potential autoantigen in this disease. Oral tolerization to autoantigens suppresses animal models of T cell-mediated autoimmune disease, including two models of rheumatoid arthritis. In this randomized, double-blind trial involving 60 patients with severe, active rheumatoid arthritis, a decrease in the number of swollen joints and tender joints occurred in subjects fed chicken type II collagen for 3 months but not in those that received a placebo. Four patients in the collagen group had complete remission of the disease. No side effects were evident. These data demonstrate clinical efficacy of an oral tolerization approach for rheumatoid arthritis.

Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus.

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Genetic susceptibility confers significant risk for systemic lupus erythematosus (SLE). The MHC region and other polymorphic loci have been associated with SLE. Because more compelling evidence for an involvement of a genetic locus includes linkage, we tested a candidate region homologous to a murine SLE susceptibility region in 52 SLE-affected sibpairs from three ethnic groups. We analyzed seven microsatellite markers from the human chromosome 1q31-q42 region corresponding to the telomeric end of mouse chromosome 1, the region where specific manifestations of murine lupus, including glomerulonephritis and IgG antichromatin, have been mapped. Comparing the mean allele sharing in affected sibpairs of each of these seven markers to their expected values of 0.50, only the five markers located at 1q41-q42 showed evidence for linkage ($P = 0.0005-0.08$). Serum levels of IgG antichromatin also showed evidence for linkage to two of these five markers ($P = 0.04$), suggesting that this phenotype is conserved between mice and humans. Compared to the expected random distribution, the trend of increased sharing of haplotypes was observed in affected sibpairs from three ethnic groups ($P < 0.01$). We concluded that this candidate 1q41-q42 region probably contains a susceptibility gene(s) that confers risk for SLE in multiple ethnic groups.

Dehydroepiandrosterone in systemic lupus erythematosus.

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Rheum Dis Clin North Am. 2000 May;26(2):349-62.

DHEA has shown promise for the treatment of SLE in three controlled and several uncontrolled clinical trials, including one large multicenter study comprising nearly 200 patients. The main benefits of DHEA seem to be a decrease in corticosteroid requirements and improved overall symptomatology. Intriguing aspects of DHEA treatment in SLE that require further study are a possible bone protective effect and improvements in cognitive function. The most frequent side effect is mild acneiform dermatitis, and long-term concerns include lowered HDL cholesterol.

The Lupus Book 1995.

Wallace, D.

New York: Oxford University Press.

Exogenous dehydroepiandrosterone modified the expression of T helper-related cytokines in NZB/NZW F1 mice.

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The onset of lupus-like disease in NZB/NZW F1 mice was correlated with the expression of IL-10 at 4 m of age, and with a sequential enhanced expression of IFN-gamma and IL-6 between 6 to 8 m of age. The expression of IFN-gamma and IL-6 was associated with exacerbation of disease symptom, production of anti-DNA antibody, and increase in total serum IgG1. Exogenous dehydroepiandrosterone (DHEA) given in animal diet significantly prolonged survival, and delayed formation of autoantibody of NZB/NZW F1 mice as compared to mice fed on control diet. The effect of DHEA paralleled a delay in the expression of IL-10 and IL-6 and an earlier detection of IL-12 transcripts. Moreover, DHEA-fed mice had higher serum IgG2a level than control diet-fed mice. Collectively, DHEA may modify the activation of distinct subset of T helper cells in NZB/NZW F1 mice at different phases of disease progression.

Effect of theanine, r-glutamylethylamide, on brain monoamines and striatal dopamine release in conscious rats.

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Neurochem Res. 1998 May;23(5):667-73.

Theanine, r-glutamylethylamide, is one of the major components of amino acids in Japanese green tea. Effect of theanine on brain amino acids and monoamines, and the striatal release of dopamine (DA) was investigated. Determination of amino acids in the brain after the intragastric administration of theanine showed that theanine was incorporated into brain through blood-brain barrier via leucine-preferring transport system. The concentrations of norepinephrine, 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindole acetic acid (5HIAA) in the brain regions were unaffected by the theanine administration except in striatum. Theanine administration caused significant increases in serotonin and/or DA concentrations in the brain, especially in striatum, hypothalamus and hippocampus. Direct administration of theanine into brain striatum by microinjection caused a significant increase of DA release in a dose-dependent manner. Microdialysis of brain with calcium-free Ringer buffer attenuated the theanine-induced DA release. Pretreatment with the Ringer buffer containing an antagonist of non-NMDA (N-methyl-D-aspartate) glutamate receptor, MK-801, for 1 hr did not change the significant increase of DA release induced by theanine. However, in the case of pretreatment with AP-5, (+/-)-2-amino-5-phosphonopentanoic acid; antagonist of NMDA glutamate receptor, the theanine-induced DA release from striatum was significantly inhibited. These results suggest that theanine might affect the metabolism and/or the release of some neurotransmitters in the brain, such as DA.

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