12. Constipation

Preventative and curative options include:

Ascorbic acid, magnesium oxide, pantothenic acid, green tea, chitosan, guar gum, pectin, psyllium, l-arginine, ferrous gluconate.

Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group.

Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Registre Bourguignon des Tumeurs Digestives, Faculte de Medecine de Dijon, France.

Lancet 2000 Oct 14;356(9238):1300-6

BACKGROUND: Some epidemiological studies have suggested that high dietary intake of calcium and fibre reduces colorectal carcinogenesis. Available data are not sufficient to serve as a basis for firm dietary advice. We undertook a multicentre randomised trial to test the effect of diet supplementation with calcium and fibre on adenoma recurrence. METHODS: We randomly assigned 665 patients with a history of colorectal adenomas to three treatment groups, in a parallel design: calcium gluconolactate and carbonate (2 g elemental calcium daily), fibre (3.5 g ispaghula husk), or placebo. Participants had colonoscopy after 3 years of follow-up. The primary endpoint was adenoma recurrence. Analyses were by intention to treat. FINDINGS: 23 patients died, 15 were lost to follow-up, 45 refused repeat colonoscopy, and five developed severe contraindications to colonoscopy. Among the 552 participants who completed the follow-up examination, 94 stopped treatment early. At least one adenoma developed in 28 (15.9%) of 176 patients in the calcium group, 58 (29.3%) of 198 in the fibre group, and 36 (20.2%) of 178 in the placebo group. The adjusted odds ratio for recurrence was 0.66 (95% CI 0.38-1.17; p=0.16) for calcium treatment and 1.67 (1.01-2.76, p=0.042) for the fibre treatment. The odds ratio associated with the fibre treatment was significantly higher in participants with baseline dietary calcium intake above the median than in those with intake below the median (interaction test, p=0.028) INTERPRETATION: Supplementation with fibre as ispaghula husk may have adverse effects on colorectal adenoma recurrence, especially in patients with high dietary calcium intake. Calcium supplementation was associated with a modest but not significant reduction in the risk of adenoma recurrence.

A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation.

Dettmar PW, Sykes J. Reckitt & Colman Products Ltd, Hull, UK.

Curr Med Res Opin 1998;14(4):227-33

An open, multi-centre study in general practice compared with efficacy, speed of action and acceptability of ispaghula husk (Fybogel Orange, Reckitt & Colman Products, UK), lactulose and other laxatives in the treatment of patients with simple constipation. A total of 65 GPs recruited 394 patients, of whom 224 (56.9%) were assigned to treatment with ispaghula and 170 (43.1%) to other laxatives (mainly lactulose) for up to four weeks. Thirteen patients withdrew before treatment started, so that 381 entered the study. Patients were assessed by their GP before entry and after two and four weeks of treatment. Patients also kept daily records of their bowel movements. After four weeks' treatment, ispaghula husk was assessed by the GPs to be superior to the other treatments in improving bowel function and in overall effectiveness, palatability and acceptability. Patients' reports of time to first bowel movement showed little difference between the treatments. Over 60% of patients in each treatment group passed a first motion within 24 hours, and over 80% within 36 hours. Ispaghula husk produced a higher percentage of normal, well-formed stools and fewer hard stools than other laxatives. Incidences of soiling, diarrhoea and abdominal pain were lower in the group receiving ispaghula husk. Overall, ispaghula husk was an effective treatment for simple constipation, and was associated with better stool consistency and a lower incidence of adverse events compared with lactulose or with other laxatives.

The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig.

Hills JM, Aaronson PI. Smith Kline Beecham Pharmaceuticals Ltd., Welwyn, Herts, England.

Gastroenterology 1991 Jul;101(1):55-65

An investigation of the mechanism of peppermint oil action was performed using isolated pharmacological preparations from guinea pig large intestine and patch clamp electrophysiology techniques on rabbit jejunum. Peppermint oil relaxed carbachol-contracted guinea pig taenia coli (IC50, 22.1 micrograms/mL) and inhibited spontaneous activity in the guinea pig colon (IC50, 25.9 micrograms/mL) and rabbit jejunum (IC50, 15.2 micrograms/mL). Peppermint oil markedly attenuated contractile responses in the guinea pig taenia coli to acetylcholine, histamine, 5-hydroxytryptamine, and substance P. Peppermint oil reduced contractions evoked by potassium depolarization and calcium contractions evoked in depolarizing Krebs solutions in taenia coli. Potential-dependent calcium currents recorded using the whole cell clamp configuration in rabbit jejunum smooth muscle cells were inhibited by peppermint oil in a concentration-dependent manner. Peppermint oil both reduced peak current amplitude and increased the rate of current decay. The effect of peppermint oil resembled that of the dihydropyridine calcium antagonists. It is concluded that peppermint oil relaxes gastrointestinal smooth muscle by reducing calcium influx.

The osmotic and intrinsic mechanisms of the pharmacological laxative action of oral high doses of magnesium sulphate. Importance of the release of digestive polypeptides and nitric oxide.

Izzo AA; Gaginella TS; Capasso F Department of Experimental Pharmacology, University of Naples Federico II, Italy.

Magnes Res (England) Jun 1996, 9 (2) p133-8

A common use for high doses of oral magnesium salts is to produce a laxative effect to treat constipation. In the intestinal lumen the poorly absorbable magnesium ions (and other ions such as sulphate) exert an osmotic effect and cause water to be retained in the intestinal lumen. This increases the fluidity of the intraluminal contents and results in a laxative action. Although the laxative action of magnesium is thought to be due to a local effect in the intestinal tract, it is also possible that released hormones such as cholecystokinin or activation of constitutive nitric oxide synthase might contribute to this pharmacological effect. Under normal circumstances the pharmacological administration of high doses of oral magnesium salts is safe and some salts--such as magnesium hydroxide--also have an antacid effect to neutralize stomach acid. However, high doses of magnesium or prolonged use may allow sufficient absorption into the systemic circulation to cause renal or other organ toxicity.

Chitosan And Fat Absorption

Kanauchi O; Deuchi K; Imasato Y; Shizukuishi M; Kobayashi E Applied Bioresearch Center, Kirin Brewery Co. Ltd., Gunma, Japan. Biosci Biotechnol Biochem (JAPAN) May 1995, 59 (5) p786-90 We investigated the mechanism for the inhibition of fat digestion by chitosan, and the synergistic effect of ascorbate. The important inhibition characteristics of fat digestion by chitosan from observations of the ileal contents were that it dissolved in the stomach and then changed to a gelled form, entrapping fat in the intestine. The synergistic effect of ascorbate (AsA) on the inhibition of fat digestion by chitosan is thought not to be acid-dependent but due to the specificity of AsA itself, according to the data resulting from using preparations supplemented with sodium ascorbate (AsN). The mechanism for the synergistic effect is considered to be 1) viscosity reduction in the stomach, which implies that chitosan mixed with a lipid is better than chitosan alone, 2) an increase in the oil-holding capacity of the chitosan gel, and 3) the chitosan-fat gel being more flexible and less likely to leak entrapped fat in the intestinal tract.

[Magnesium: current concepts of its physiopathology, clinical aspects and therapy]

Mancinella A, Bartolucci E.

Acta Vitaminol Enzymol (Italy) 1982, 4 (1-2) p87-97

Functional constipation is not a life-threatening disease, but as a chronic state it worries the patient and causes him discomfort and often leads him to self-medication with potentially dangerous drugs. Ro 01-4709 contains as active substance dexpanthenol, which is the alcohol of pantothenic acid, a vitamin of the B-complex. In the cells, dexpanthenol is readily oxidized to pantothenic acid, which stimulates peristalsis when administered in therapeutically effective doses.

Ro 01-4709 has already proven its efficacy in the prevention and treatment of adynamic ileus. Recently, several open and two double-blind studies have been carried out, investigating the efficacy of oral Ro 01-4709 in the treatment of chronic functional constipation. The two double-blind studies showed Ro 01-4709 to be superior to placebo in all parameters measured. The studies with an open design also demonstrated a favourable effect of Ro 01-4709 in the treatment of chronic functional constipation. Owing to its physiological action-which is in a favourable contrast to that of normal laxatives. Ro 01-4709 can be recommended for the treatment of functional constipation in pregnant women, children and the elderly.

Fat binder: a study of safety in obese patients.

Rossner S, Abelin J:

MATS Medical AB, Stockholm, Sweden, 1995.

Abstract: L112 Biopolymer (L112 Fat Blocker) is an investigational drug extracted from shellfish. L112 Biopolymer has unique properities in its ability of binding fat from the food in the stomach and in the intestines. This leads to a correction and normalization of the LDL cholesterol and triglyceride levels in the blood. The HDL-cholesterol level in the blood increases. The fat sucked out of the food and remains in the digestional canal. Thus the blood takes up less fat which leads to less fat deposits in the body. The body absorbs fewer calories from the fat and the cholesterol and triglyceride levels in the blood are reduced, all in one natural process. L112 Fat Blocker is made of a special fibre-like substance derived from the shells of shrimps, crabs and ohter shellfishes. After chemical extraction the substances has got electrostatic properties and has unique fat binding properties. It has been tested by a Norwegian research laboratory. When given orally together with the food it immediately disperse into tiny particles. These have great affinity to fat and starts binding themselves to fat particles in the stomach and upper intestines. With increasing pH in the lower intestines the binding occurs probably through precipitation and the body cannot any longer absorb the fat through the intestinal wall or dispense the into the blood stream. The substances has been tested in clinical trials and shows a remarkable effect in reducing total cholesterol while allowing the HDL-cholesterol to increase. In one randomized double-blind study with placebo-control the weight reduction was 2.5 times better than diet alone. A preliminary review on L112 Biopolymer has been published elsewhere. When fat contents in the bowel increases, it makes the feces soft and smooth. This may be particularly positive for those who suffer from obstipation. In this unicentre trial the fat content in feces and laboratory parameters, during treatment with L112 twice daily, will be investigated.

[A clinical study of the use of a combination of glucomannan with lactulose in the constipation of pregnancy]

Signorelli P; Croce P; Dede A Divisione di Ostetricia e Ginecologia, Ospedale di Codogno, Regione Lombardia, USL n. 25, Lodi.

Minerva Ginecol (Italy) Dec 1996, 48 (12) p577-82

RATIONAL: Constipation is a problem frequently encountered during pregnancy as is excessive weight gain. Treatments of common use to control constipation are endowed with some drawbacks and they are not active in controlling weight increase. A preparation of lactulose and glucomannan in previous studies proved very effective and well tolerated in patients affected by stypsis and evidentiated also activity both in controlling excessive food intake and in correcting some metabolic imbalances regarding lipids and urea.

MATERIAL AND METHODS: 50 pregnant females affected by constipation were treated with sachets containing a preparation of glucomannan (1.45 g) and lactulose (4.2 g) in a posology of 2 (1-4) sachets a day for 1-3 months.

RESULTS: Treatment induced a return to normal frequency of weekly number of evacuations (4.9-5.8/week) and a parallel control of weight gain (within 20% of initial body weight). The latter finding seems to be related to hunger control induced by glucomannan at the gastric level which prevents an excessive food intake.

Analysis of two novel classes of plant antifungal proteins from radish (Raphanus sativus L.) seeds.

Terras FR, Schoofs HM, De Bolle MF, Van Leuven F, Rees SB, Vanderleyden J, Cammue BP, Broekaert WF. F. A. Janssens Laboratory of Genetics, Catholic University of Leuven, Heverlee, Belgium.

J Biol Chem 1992 Aug 5;267(22):15301-9

Two novel classes of antifungal proteins were isolated from radish seeds. The first class consists of two homologous proteins (Rs-AFP1 and Rs-AFP2) that were purified to homogeneity. They are highly basic oligomeric proteins composed of small (5-kDa) polypeptides that are rich in cysteine. Both Rs-AFPs have a broad antifungal spectrum and are among the most potent antifungal proteins hitherto characterized. In comparison with many other plant antifungal proteins, the activity of the Rs-AFPs is less sensitive to the presence of cations. Moreover, their antibiotic activity shows a high degree of specificity to filamentous fungi. The amino-terminal regions of the Rs-AFPs show homology with the derived amino acid sequences of two pea genes specifically induced upon fungal attack, to gamma-thionins and to sorghum alpha-amylase inhibitors. The radish 2S storage albumins were identified as the second novel class of antifungal proteins. All isoforms inhibit growth of different plant pathogenic fungi and some bacteria. However, their antimicrobial activities are strongly antagonized by cations.

Physiological role of dietary fiber: a ten-year review.

Trowell H, Burkitt D.

ASDC J Dent Child 1986 Nov-Dec;53(6):444-7

It is accepted nowadays that dietary fiber is an important constituent of the diet. There is growing evidence that the low fiber Western diets and the low

consumption of whole grain products are important factors in several common diseases of the large bowel. Cereal fiber differs from that present in vegetables and fruit. A low intake of cereal fiber has been implicated in cancer of the large bowel, diverticular disease of the colon and coronary heart disease. High fiber diets are often prescribed for diabetes. Although fiber consumption by British and American consumers has decreased over the past century, consumption of whole wheat breads and fiber-rich breakfast cereals has received new attention during the past ten years.

Clinical response to dietary fiber treatment of chronic constipation.

Voderholzer WA; Schatke W; Muhldorfer BE; Klauser AG; Birkner B; Muller-Lissner SA Medizinische Klinik, Klinikum Innenstadt, University of Munich, Germany.

Am J Gastroenterol (United States) Jan 1997, 92 (1) p95-8

OBJECTIVES: To determine the clinical outcome of dietary fiber therapy in patients with chronic constipation.

METHODS: One hundred, forty-nine patients with chronic constipation (age 53 yr, range 18-81 yr, 84% women) at two gastroenterology departments in Munich, Germany, were treated with Plantago ovata seeds, 15-30 g/day, for a period of at least 6 wk. Repeated symptom evaluation, oroanal transit time measurement (radiopaque markers), and functional rectoanal evaluation (proctoscopy, manometry, defecography) were performed. Patients were classified on the basis of the result of dietary fiber treatment: no effect, n = 84; improved, n = 33; and symptom free, n = 32.

RESULTS: Eighty percent of patients with slow transit and 63% of patients with a disorder of defecation did not respond to dietary fiber treatment, whereas 85% of patients without a pathological finding improved or became symptom free.

CONCLUSION: Slow GI transit and/or a disorder of defecation may explain a poor outcome of dietary fiber therapy in patients with chronic constipation. A dietary fiber trial should be conducted before technical investigations, which are indicated only if the dietary fiber trial fails.

Mechanisms of constipation in older persons and effects of fiber compared with placebo.

Cheskin LJ, Kamal N, Crowell MD, Schuster MM, Whitehead WE Division of Digestive Diseases, Johns Hopkins Bayview Medical Center, Baltimore, MD 21224, USA. J Am Geriatr Soc 1995 Jun;43(6):666-9

OBJECTIVE: To investigate the mechanisms of constipation and the effect of fiber supplementation on physiology, mechanisms, stool parameters, and colonic transit times in a group of constipated older patients.

DESIGN: Single-blind, randomized, placebo-controlled fiber intervention with crossover.

SETTING: A university-based outpatient center.

PATIENTS: Ten community-living older men and women, healthy except for chronic constipation.

INTERVENTIONS: Patients were given either 24 g psyllium fiber or placebo fiber daily for 1 month, then crossed over to the other arm for an additional month. Structured testing, including total gut transit time and rectal and colonic manometry, was performed at the end of each intervention month. Patients recorded stool frequency, consistency, and weights daily.

RESULTS: The predominant mechanism for constipation in these patients was outlet delay caused by pelvic dyssynergia. Fiber decreased total gut transit time from 53.9 hours (placebo condition) to 30.0 hours (< .05). stool weights and consistency were not significantly improved by fiber, though there was a trend toward an increase in stool frequency (1.3 vs 0.8 bowel movements per day.) Pelvic floor dyssynergia was not remedied by fiber, even when constipation was clinically improved.

CONCLUSIONS: Fiber supplementation appeared to benefit constipated older patients clinically, and it improved colonic transit time, but it did not rectify the most frequent underlying abnormality, pelvic floor dyssynergia.

[Intake of dietary fiber and other nutrients by children with and without functional chronic constipation]

de Morais MB; Vitolo MR; Aguirre AN; Medeiros EH; Antoneli EM; Fagundes-Neto U Departamento de Pediatrica da Universidade Federal de Sao-Paulo-Escola Paulista de Medicina (UNIFESP-EPM).

Arq Gastroenterol (Brazil) Apr-Jun 1996, 33 (2) p93-101

The aim of this study was to evaluate the dietary fiber intake and the dietary habits of children with and without functional chronic constipation. We enrolled 58 children with functional chronic constipation and 58 controls without constipation matched for sex and age. Food and fiber intake were evaluated by 24 hour dietary recall and a complete clinical history was performed. The age of onset of constipation occurred during the first year of life in 55.4% of the patients while the median age of evaluation was 78 months. Soiling was found in 41.7% of patients. The median period of exclusive breast feeding was shorter (P = 0.002) in the constipation group (one month) than in the control group (three month). The proportion of constipation was similar for mothers of children of both groups as well as for siblings in both groups. The fathers of children with constipation presented higher frequency of constipation (12.3%) than the fathers of children in control group (1.8%), but the difference did not reach statistical significance (P = 0.06). The amount of food measured by 24 hour recall was similar in both groups.

The calorie intake of constipated children (1526 +/- 585 calories/day) was lower (P = 0.07) than in the control group (1712 +/- 513 calories/day) but the difference did not reach statistical significance. The intake of protein, fat and iron was lower in the constipation group than in the control group. The volume of cow's milk intake was similar in both groups. The median of total dietary fiber intake in the constipation group (13.5 g/day) was statistically (P = 0.009) lower than in the control group (16.8 g/day). The daily intake of insoluble dietary fiber was also statistically lower (P = 0.001) in the constipation group (6.3 g) than in the control group (9.4 g). The intake of soluble dietary fiber was similar in both groups. The intake of dietary fiber per 1,000 calories of diet was 10.3 g in the constipation group and 10.4 in the control group (P = 0.41). There was a considerable intersection of individual values in fiber intake of the constipation and control groups, suggesting that low fiber intake acts in association with others factors on the genesis of constipation in children. However, the low intake of insoluble fiber, suggests that it plays an important role on the pathogenesis of chronic constipation in children.

Effectiveness of bran supplement on the bowel management of elderly rehabilitation patients.

Gibson CJ; Opalka PC; Moore CA; Brady RS; Mion LC

J Gerontol Nurs (United States) Oct 1995, 21 (10) p21-30

1. Constipation is a common problem in the elderly that affects up to 20% of those 65 years and older.

2. Patients receiving the fiber supplement had a significantly lower number of bowel agents per day as compared to the control patients.

3. Side effects from the additional fiber occurred in a subgroup of patients; thus, institution of additional fiber to the diets of ill, physically dependent patients is best done gradually and with close monitoring.

Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, vitamins A and E, and minerals in geriatric hospital patients in the treatment of constipation.

Kinnunen O, Salokannel J Department of Internal Medicine, Health Centre Hospital, Oulu, Finland.

J Int Med Res 1989 Sep-Oct;17(5):442-54

In a crossover study the effects of magnesium hydroxide on serum lipids, carbohydrates, vitamins A and E, uric acid and whole blood minerals were compared with those of a bulk laxative containing plantago rind and sorbitol in 64 constipated, elderly long-stay patients, 55 of whom were receiving diuretics. Hypomagnesaemia occurred in 11 (17%) patients after bulk laxative and in two (2%) patients after magnesium hydroxide treatment. There was a slight reduction in low values of high-density lipoprotein cholesterol and high values of

triglycerides after magnesium hydroxide treatment. There were no significant differences in plasma lipids, whole blood minerals or vitamins A and E using either laxative. Negative p correlations were found between the increase in serum concentrations of magnesium and glycosylated haemoglobin A1 (P less than 0.02) and the serum level of uric acid (P less than 0.01). These results suggest that the long-term effects of magnesium hydroxide and bulk laxative on the absorption of nutrients may not be significantly different. Magnesium hydroxide, however, may have beneficial effects on lipid disorders, impaired glucose tolerance and hyperuricaemia in magnesium deficiency due to diuretics and thus may be a favourable laxative for use in bedridden geriatric patients receiving diuretics.

The connection between dietary fibre intake and chronic constipation in children

Mooren G.C.A.H.C.M.; Van Der Plas R.N.; Bossuyt P.M.M.; Taminiau J.A.J.M. ; Buller H.A. Academisch Medisch Centrum, Kinder AMC, Afd. Kindergastroenterologie/Voed ing, Meibergdreef 9, 1105 AZ Amsterdam Netherlands

Nederlands Tijdschrift voor Geneeskunde (Netherlands), 1996, 140/41 (2036-2039)

Objective. Evaluation of the feeding patterns of children with chronic constipation, in particular dietary fibres, energy and fluid intake and their influence on colonic transit time. In addition, the effect of dietary recommendations regarding fibres was assessed.

Design. Prospective randomized study.

Setting. Department of Paediatric Gastroenterology and Nutrition, Academic Medical Centre, Amsterdam, the Netherlands.

Method. Children with at least 2 months of complaints related to constipation were enrolled and both dietary intake and colonic transit time were evaluated. After dietary and laxative treatment, in some combined with biofeedback training, and a follow-up of 6 months, a randomized sample were again evaluated regarding their transit times and dietary patterns.

Results. In 73 consecutive children mean fibre intake was the same as in healthy controls, although energy and fluid intake were lower. Colonic transit time was increased compared with healthy controls and no relationship was established between fibre intake and transit time. At 6 months no significant increase in mean fibre intake was observed and no relationship was found between either transit time and change in fibre intake or cure and change in fibre intake. In the cured patients no increase of their mean fibre intake could be observed.

Conclusion. The amount of dietary fibres played no pathogenic part in chronic constipation. Dietary advice did not change the mean fibre content of the diet. In addition, changes in fibre intake had no effect on colonic transit time or cure.

Dietary fiber and laxation in postop orthopedic patients.

Ouellet LL; Turner TR; Pond S; McLaughlin H; Knorr S Clin Nurs Res (United States) Nov 1996, 5 (4) p428-40

The addition of wheat fiber in the diet of post-surgical orthopedic patients as a means of preventing constipation was studied using a quasi-experimental design. It was hypothesized that a 20 gm supplement of All Bran and natural bran would promote spontaneous bowel movements, reduce the incidence of constipation, and thus decrease the need for elimination interventions. The results show that the study group had more spontaneous bowel movements and required fewer elimination interventions than did the control group.

[Intake of dietary fiber and other nutrients by children with and without functional chronic constipation]

de Morais MB; Vitolo MR; Aguirre AN; Medeiros EH; Antoneli EM; Fagundes-Neto U
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[A clinical study of the use of a combination of glucomannan with lactulose in the constipation of pregnancy]

Signorelli P; Croce P; Dede A
Divisione di Ostetricia e Ginecologia, Ospedale di Codogno, Regione Lombardia, USL n. 25, Lodi.
Minerva Ginecol (Italy) Dec 1996, 48 (12) p577-82

RATIONAL: Constipation is a problem frequently encountered during pregnancy as is excessive weight gain. Treatments of common use to control constipation are endowed with some drawbacks and they are not active in controlling weight increase. A preparation of lactulose and glucomannan in previous studies proved very effective and well tolerated in patients affected by stypsis and evidentiated also activity both in controlling excessive food intake and in correcting some metabolic imbalances regarding lipids and urea.

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RESULTS: Treatment induced a return to normal frequency of weekly number of evacuations (4.9-5.8/week) and a parallel control of weight gain (within 20% of initial body weight). The latter finding seems to be related to hunger control induced by glucomannan at the gastric level which prevents an excessive food intake.

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[The relationship between intake of dietary fiber and chronic constipation in children]

Mooren GC; van der Plas RN; Bossuyt PM; Taminiau JA; Buller HA
Academisch Medisch Centrum-Het Kinder AMC, afd Kindergastroenterologie en Voeding, Amsterdam.
Ned Tijdschr Geneeskd (Netherlands) Oct 12 1996, 140 (41) p2036-9

OBJECTIVE: Evaluation of the feeding patterns of children with chronic constipation, in particular dietary fibres, energy and fluid intake and their influence on colonic transit time. In addition, the effect of dietary recommendations regarding fibres was assessed.

DESIGN: Prospective randomized study.

SETTING: Department of Paediatric Gastroenterology and Nutrition, Academic Medical Centre, Amsterdam, the Netherlands.

METHOD: Children with at least 2 months of complaints related to constipation were enrolled and both dietary intake and colonic transit time were evaluated. After dietary and laxative treatment, in some combined with biofeedback training, and a follow-up of 6 months, a randomized sample were again evaluated regarding their transit times and dietary patterns.

RESULTS: In 73 consecutive children mean fibre intake was the same as in healthy controls, although energy and fluid intake were lower. Colonic transit time was increased compared with healthy controls and no relationship was established between fibre intake and transit time. At 6 months no significant increase in mean fibre intake was observed and no relationship was found between either transit time and change in fibre intake or cure and change in fibre intake. In the cured patients no increase of their mean fibre intake could be observed.

CONCLUSION: The amount of dietary fibres played no pathogenic part in chronic constipation. Dietary advice did not change the mean fibre content of the diet. In addition, changes in fibre intake had no effect on colonic transit time or cure.

Assessment of the effect of increased dietary fibre intake on bowel function in patients with spinal cord injury.

Cameron KJ; Nyulasi IB; Collier GR; Brown DJ
Spinal Injuries Unit, Austin Hospital, Heidelberg, Victoria, Australia.
Spinal Cord (England) May 1996, 34 (5) p277-83

It is common for constipation to occur following severe spinal cord injury (SCI). Although a bowel management program including a high fibre diet is an integral part of rehabilitation, the effect of a high fibre diet on large bowel function in SCI has not been examined. The aims of this study were to assess the nutrient intake of SCI patients, to determine baseline transit time, stool weight and evacuation

time and to assess the effect of addition of bran on large bowel function. Eleven subjects, aged 32 +/- 10.5 years participated in the study. The level of injury ranged from C4 to T12; only one patient had an incomplete injury. Baseline mean energy intake was 7823 +/- 1443 kJ/d, protein intake 93 +/- 21 g/d, carbohydrate intake 209 +/- 39 g/d and mean dietary fibre intake 25 +/- 8 g/d. Mean baseline stool weight was 128 +/- 55 g/d and bowel evacuation time was 13 +/- 7.4 min/d. Three subjects who consumed < 18 g dietary fibre/d had low stool weights of 60-70 g/d and two had very delayed transit times that were too slow to enable quantitation. Mean mouth to anus transit time was 51.3 +/- 31.2 h, mean colonic transit time 28.2 +/- 3.5 h, right colonic transit time 5.9 +/- 4.5 h, left colonic transit time 14.5 +/- 5.2 h and rectosigmoid colonic transit time 7.9 +/- 5.6 h. Following the addition of bran, dietary fibre intake significantly increased from 25 g/d to 31 g/d ($P < 0.001$). However, the mean colonic transit time increased from 28.2 h to 42.2 h ($P < 0.05$) and rectosigmoid colon transit time increased from 7.9 to 23.3 h ($P < 0.02$). Stool weight, mouth to anus, left and right colon transit time and evacuation time did not change significantly. Results of this study suggest that increasing dietary fibre in SCI patients does not have the same effect on bowel function as has been previously demonstrated in individuals with 'normally functioning' bowels. Indeed the effect may be the opposite to that desired. This preliminary study highlights the need for further research to examine the optimal level of dietary fibre intake in SCI patients.

Therapeutic availability of iron administered orally as the ferrous gluconate together with magnesium-L-aspartate hydrochloride.

Disch G; Classen HG; Spatling L; Leifert U; Schumacher E
Department of Pharmacology and Toxicology of Nutrition, University of Hohenheim, Stuttgart-Hohenheim, Germany.
Arzneimittelforschung (Germany) Mar 1996, 46 (3) p302-6

Since in vitro experiments had excluded interactions between Fe-gluconate (Fe-gluc) and magnesium-L-aspartate hydrochloride (MAH) in aqueous solutions the present in vivo studies seemed to be justified. Animal studies: Rats were kept on magnesium-(Mg)- and iron-(Fe)- sufficient and deficient diets. The intragastral administration of Fe-gluc significantly increased plasma Fe after 3 h, either given alone, or in combination with MAH (inducing hypermagnesemia). Same results were obtained when fortified diets were offered to Fe/Mg-deficient animals. Human studies: The combination of Fe-gluc (2 x 50 mg Fe per day, per os) plus MAH (2 x 7.5 mmol Mg per day, p.o.) was well tolerated by healthy volunteers. Single dose experiments revealed that Fe-gluc alone and in combination with MAH increased plasma Fe levels during 3 h to the same extent. Two groups of pregnant women with moderately reduced hemoglobin levels either received Fe-gluc (out-patients) or its combination with MAH (at least temporarily hospitalised because of preterm labor). Treatments were well tolerated. Hemoglobin levels did not further decrease, as expected without Fe supplements, during the course of pregnancy, thus indicating the therapeutic availability of the electrolytes in both study groups. Progesterone-induced constipation is frequently observed during

pregnancy; hence stool softening reported by 50% of the women receiving Fe-gluc plus MAH (versus 33% in the Fe-gluc group) can be regarded as desirable effect. It is concluded that MAH does not interfere with the enteral absorption of Fe-gluc when both electrolytes are orally administered together. Taking both electrolytes together instead of 2 to 3 h apart from each other, as actually recommended, means a less complicated dosage regimen and probably improves compliance.

The osmotic and intrinsic mechanisms of the pharmacological laxative action of oral high doses of magnesium sulphate. Importance of the release of digestive polypeptides and nitric oxide.

Izzo AA; Gaginella TS; Capasso F
Department of Experimental Pharmacology, University of Naples Federico II, Italy.
Magnes Res (England) Jun 1996, 9 (2) p133-8

A common use for high doses of oral magnesium salts is to produce a laxative effect to treat constipation. In the intestinal lumen the poorly absorbable magnesium ions (and other ions such as sulphate) exert an osmotic effect and cause water to be retained in the intestinal lumen. This increases the fluidity of the intraluminal contents and results in a laxative action. Although the laxative action of magnesium is thought to be due to a local effect in the intestinal tract, it is also possible that released hormones such as cholecystokinin or activation of constitutive nitric oxide synthase might contribute to this pharmacological effect. Under normal circumstances the pharmacological administration of high doses of oral magnesium salts is safe and some salts--such as magnesium hydroxide--also have an antacid effect to neutralize stomach acid. However, high doses of magnesium or prolonged use may allow sufficient absorption into the systemic circulation to cause renal or other organ toxicity. (35

Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, vitamins A and E, and minerals in geriatric hospital patients in the eatment of constipation.

Kinnunen O, Salokannel J
Department of Internal Medicine, Health Centre Hospital, Oulu, Finland.
J Int Med Res 1989 Sep-Oct;17(5):442-54

In a crossover study the effects of magnesium hydroxide on serum lipids, carbohydrates, vitamins A and E, uric acid and whole blood minerals were compared with those of a bulk laxative containing plantago rind and sorbitol in 64 constipated, elderly long-stay patients, 55 of whom were receiving diuretics. Hypomagnesaemia occurred in 11 (17%) patients after bulk laxative and in two (2%) patients after magnesium hydroxide treatment. There was a slight reduction in low values of high-density lipoprotein cholesterol and high values of

triglycerides after magnesium hydroxide treatment. There were no significant differences in plasma lipids, whole blood minerals or vitamins A and E using either laxative. Negative p correlations were found between the increase in serum concentrations of magnesium and glycosylated haemoglobin A1 (P less than 0.02) and the serum level of uric acid (P less than 0.01). These results suggest that the long-term effects of magnesium hydroxide and bulk laxative on the absorption of nutrients may not be significantly different. Magnesium hydroxide, however, may have beneficial effects on lipid disorders, impaired glucose tolerance and hyperuricaemia in magnesium deficiency due to diuretics and thus may be a favourable laxative for use in bedridden geriatric patients receiving diuretics.

[Magnesium: current concepts of its physiopathology, clinical aspects and therapy]

Acta Vitaminol Enzymol (Italy) 1982, 4 (1-2) p87-97

Functional constipation is not a life-threatening disease, but as a chronic state it worries the patient and causes him discomfort and often leads him to self-medication with potentially dangerous drugs. Ro 01-4709 contains as active substance dexpanthenol, which is the alcohol of pantothenic acid, a vitamin of the B-complex. In the cells, dexpanthenol is readily oxidized to pantothenic acid, which stimulates peristalsis when administered in therapeutically effective doses. Ro 01-4709 has already proven its efficacy in the prevention and treatment of adynamic ileus. Recently, several open and two double-blind studies have been carried out, investigating the efficacy of oral Ro 01-4709 in the treatment of chronic functional constipation. The two double-blind studies showed Ro 01-4709 to be superior to placebo in all parameters measured. The studies with an open design also demonstrated a favourable effect of Ro 01-4709 in the treatment of chronic functional constipation. Owing to its physiological action-which is in a favourable contrast to that of normal laxatives. Ro 01-4709 can be recommended for the treatment of functional constipation in pregnant women, children and the elderly.

Endogenous nitric oxide modulates morphine-induced constipation.

Calignano A, Moncada S, Di Rosa M
Department of Experimental Pharmacology, University of Naples Federico II, Italy.
Biochem Biophys Res Commun 1991 Dec 16;181(2):889-93

Administration of morphine in mice causes inhibition of the gastrointestinal transit of a charcoal meal. Morphine-induced constipation in mice seems to depend predominantly on action(s) on the central nervous system since N-methyl morphine, a quaternary derivative, inhibits intestinal transit only when administered intracerebroventricularly (i.c.v.). L- but not D-arginine, given intraperitoneally, reversed the constipation induced by both morphine and its

quaternary analogue. L-arginine was ineffective when given i.c.v. and did not reverse atropine-induced constipation. These results suggest that L-arginine preferentially modulates opioid-induced constipation through a stereospecific and peripheral action(s). It is possible that the effect of L-arginine is achieved by increasing the amount of nitric oxide released by non-adrenergic, non-cholinergic nerves in the gut. Thus, L-arginine may represent a useful agent for the treatment of undesirable constipation associated with the use of narcotic analgesics.

13. Depression

Preventative and curative options include:

SAMe, DHEA, pregnenolone, *dl*-phenylalanine, DMAE, vitamin B5, tyrosine, l-carnitine, NADH, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B12, choline, folic acid, vitamin C, potassium, St. John's wort, ginseng, ginkgo biloba, fish oil.

Nutrition and depression: the role of folate.

Alpert JE, Fava M. Department of Psychiatry, Harvard Medical School, Boston, MA 02114, USA.

Nutr Rev 1997 May;55(5):145-9

A relationship between folate and neuropsychiatric disorders has been inferred from clinical observation and from the enhanced understanding of the role of folate in critical brain metabolic pathways. Depressive symptoms are the most common neuropsychiatric manifestation of folate deficiency. Conversely, borderline low or deficient serum or red blood cell folate levels have been detected in 15-38% of adults diagnosed with depressive disorders. Recently, low folate levels have been linked to poorer antidepressant response to selective serotonin reuptake inhibitors. Factors contributing to low serum folate levels among depressed patients as well as the circumstances under which folate and its derivatives may have a role in antidepressant pharmacotherapy must be further clarified.

Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction.

Bell IR, Edman JS, Morrow FD, Marby DW, Perrone G, Kayne HL, Greenwald M, Cole JO. Department of Psychiatry, Harvard Medical School.

J Am Coll Nutr 1992 Apr;11(2):159-63

This was a 4-week randomized placebo-controlled double-blind study to assess augmentation of open tricyclic antidepressant treatment with 10 mg each of vitamins B1, B2, and B6 in 14 geriatric inpatients with depression. The active vitamin group demonstrated significantly better B2 and B6 status on enzyme activity coefficients and trends toward greater improvement in scores on ratings of depression and congnitive function, as well as in serum nortriptyline levels compared with placebo-treated subjects (Ss). Without specific supplementation, B12 levels increased in Ss receiving B1/B2/B6 and decreased in placebo Ss.

These findings offer preliminary support for further investigation of B complex vitamin augmentation in the treatment of geriatric depression.

Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine

Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H Special Studies Clinic, Mexican Institute of Psychiatry, Tlalpan. Psychiatry Res 1992 Dec;44(3):257-62

A double-blind clinical trial was carried out to evaluate the efficacy of S-adenosyl-L-methionine (SAMe) in speeding the onset of action of imipramine (IMI). SAMe is a naturally occurring substance that has been shown to possess antidepressant activity with a rapid mode of onset and minimal side effects. Sixty-three outpatients with moderate to severe depression were included in the study. After an initial 1-week placebo period, only 40 patients entered the active treatment phase. During the first 2 weeks of the trial, half of these patients received 200 mg/day of SAMe intramuscularly, while the other half received placebo. Simultaneously, oral IMI was administered to all patients at a fixed dose of 150 mg/day. The onset of clinical response was determined by evaluating patients every second day. By the end of week 2, the parenteral treatment was suppressed and IMI was adjusted according to individual needs. Depressive symptoms decreased earlier in the patients who were receiving the SAMe-IMI combination than in those who were receiving the placebo-IMI combination.

5-Hydroxytryptophan: a clinically-effective serotonin precursor.

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Altern Med Rev 1998 Aug;3(4):271-80

5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. Intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it may be taken with meals without reducing its effectiveness. Unlike LT, 5-HTP cannot be shunted into niacin or protein production. Therapeutic use of 5-HTP bypasses the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. 5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behaviour, and pain sensation. Therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia.

L-deprenyl plus L-phenylalanine in the treatment of depression.

Birkmayer W, Riederer P, Linauer W, Knoll J.

J Neural Transm 1984;59(1):81-7

The antidepressive efficacy of 1-deprenyl (5-10 mg daily) plus 1-phenylalanine (250 mg/day) has been evaluated in 155 unipolar depressed patients. Both oral and intravenous administration showed beneficial effects in 90% of outpatients and 80.5% of inpatients. It is concluded that this combined treatment has a potent antidepressive action based on the accumulation of 1-phenylethylamine in the brain.

Dehydroepiandrosterone treatment of midlife dysthymia.

Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Behavioral Endocrinology Branch, National Institute of Mental Health, Bethesda, MD 20892-1276, USA.

Biol Psychiatry 1999 Jun 15;45(12):1533-41

BACKGROUND: This study evaluated the efficacy of the adrenal androgen, dehydroepiandrosterone, in the treatment of midlife-onset dysthymia.

METHODS: A double-blind, randomized crossover treatment study was performed as follows: 3 weeks on 90 mg dehydroepiandrosterone, 3 weeks on 450 mg dehydroepiandrosterone, and 6 weeks on placebo. Outcome measures consisted of the following. Cross-sectional self-ratings included the Beck Depression Inventory, and visual analogue symptom scales. Cross-sectional objective ratings included the Hamilton Depression Rating Scale, the Cornell Dysthymia Scale and a cognitive test battery. Seventeen men and women aged 45 to 63 years with midlife-onset dysthymia participated in this study. Response to dehydroepiandrosterone or placebo was defined as a 50% reduction from baseline in either the Hamilton Depression Rating Scale or the Beck Depression Inventory.

RESULTS: In 15 patients who completed the study, a robust effect of dehydroepiandrosterone on mood was observed compared with placebo. Sixty percent of the patients responded to dehydroepiandrosterone at the end of the 6-week treatment period compared with 20% on placebo. A significant response was seen after 3 weeks of treatment on 90 mg per day. The symptoms that improved most significantly were anhedonia, loss of energy, lack of motivation, emotional "numbness," sadness, inability to cope, and worry. Dehydroepiandrosterone showed no specific effects on cognitive function or sleep disturbance, although a type II error could not be ruled out.

CONCLUSIONS: This pilot study suggests that dehydroepiandrosterone is an effective treatment for midlife-onset dysthymia.

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.

Homocysteine, folate, methylation, and monoamine metabolism in depression.

Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Department of Neurology, King's College Hospital, London, UK.

J Neurol Neurosurg Psychiatry 2000 Aug;69(2):228-32

OBJECTIVES: Previous studies suggest that folate deficiency may occur in up to one third of patients with severe depression, and that treatment with the vitamin may enhance recovery of the mental state. There are, however, difficulties in interpreting serum and red cell folate assays in some patients, and it has been suggested that total plasma homocysteine is a more sensitive measure of functional folate (and vitamin B12) deficiency. Other studies suggest a link between folate deficiency and impaired metabolism of serotonin, dopamine, and noradrenaline (norepinephrine), which have been implicated in mood disorders. A study of homocysteine, folate, and monoamine metabolism has, therefore, been undertaken in patients with severe depression.

METHODS: In 46 inpatients with severe DSM III depression, blood counts, serum and red cell folate, serum vitamin B12, total plasma homocysteine, and, in 28 patients, CSF folate, S-adenosylmethionine, and the monoamine neurotransmitter metabolites 5HIAA, HVA, and MHPG were examined. Two control groups comprised 18 healthy volunteers and 20 patients with neurological disorders, the second group undergoing CSF examination for diagnostic purposes.

RESULTS: Twenty four depressed patients (52%) had raised total plasma homocysteine. Depressed patients with raised total plasma homocysteine had significant lowering of serum, red cell, and CSF folate, CSF S-adenosylmethionine and all three CSF monoamine metabolites. Total plasma homocysteine was significantly negatively correlated with red cell folate in depressed patients, but not controls.

CONCLUSIONS: Utilising total plasma homocysteine as a sensitive measure of functional folate deficiency, a biological subgroup of depression with folate deficiency, impaired methylation, and monoamine neurotransmitter metabolism has been identified. Detection of this subgroup, which will not be achieved by routine blood counts, is important in view of the potential benefit of vitamin replacement.

Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study.

Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. St. John's Episcopal Hospital, Far Rockaway, New York 11691, USA.

Clin Ther 2000 Apr;22(4):411-9

BACKGROUND: Hypericum (St. John's wort) has been shown to be as efficacious and well tolerated as standard antidepressants in the treatment of depression but has not been compared with selective serotonin reuptake inhibitors (SSRIs).

OBJECTIVE: This study compared hypericum and the SSRI sertraline in the treatment of depression.

METHODS: In a double-blind, randomized study conducted in a community hospital, 30 male and female outpatients (19 women, 11 men; mean age, 45.5 years) with mild to moderate depression received 600 mg/d of a standardized extract of hypericum (LI 160) or 50 mg/d sertraline for I week, followed by hypericum 900 mg/d or sertraline 75 mg/d for 6 weeks.

RESULTS: The severity of symptoms, as assessed by scores on the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression scale, was significantly reduced in both treatment groups (< 0.01). Clinical response (defined as a < or =50% reduction in HAM-D scores) was noted in 47% of patients receiving hypericum and 40% of those receiving sertraline. The difference was not statistically significant. Both agents were well tolerated. A post hoc power analysis indicated that failure to reach statistical significance between treatments resulted primarily from an absence of clinical differences rather than the small sample size.

CONCLUSION: The hypericum extract was at least as effective as sertraline in the treatment of mild to moderate depression in a small group of outpatients.

S-adenosyl-l-methionine (SAMe) as antidepressant: Meta-analysis of clinical studies

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Acta Neurol Scand Suppl 1994;154:7-14

Introduction - S-adenosyl-l-methionine (SAMe) is a naturally-occurring substance which is a major source of methyl groups in the brain. Material and methods - We conducted a meta-analysis of the studies on SAMe to assess the efficacy of this compound in the treatment of depression compared with placebo and standard tricyclic antidepressants. Results - Our meta-analysis showed a greater response rate with SAMe when compared with placebo, with a global effect size ranging from 27% to 38% depending on the definition of response, and an antidepressant effect comparable with that of standard tricyclic antidepressants. Conclusion - The efficacy of SAMe in treating depressive syndromes and disorders is superior with that of placebo and comparable to that of standard tricyclic antidepressants. Since SAMe is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression.

[Effect of pyridoxine on the psychopathology and pathochemistry of involutional depressions] [Article in Russian]

Bukreev VI.

Zh Nevropatol Psikhiatr Im S S Korsakova 1978;78(3):402-8

In agreement with the catecholamine hypotheses of affective disorders the main role in the pathogenesis of depressive states is allocated to the central "noradrenergic insufficiency". The author thinks it feasible to use pyridoxine (vit. B6) in the treatment of depressive states, inasmuch as it is involved in the process of catecholamine synthesis as a cofactor of DOPA-decarboxylase. The author examined 48 patients among which 31 were with involutional melancholia and 17 with manic-depressive psychoses, manifesting after 40 years. Along with a positive therapeutical effect there was an increase in the noradrenaline excretion and a drop in the relative adrenaline content.

Neuropsychiatric disorders associated with nutritional deficiencies. Incidence and therapeutic implications

Carney M.W.P. Hill House, Mount Park Road,Harrow-on-the-Hill, Middlesex HA13JY United Kingdom

CNS Drugs (CNS DRUGS) (New Zealand) 1995, 3/4 (279-290) Deficiencies of various vitamins are associated with a variety of neuropsychiatric manifestations. Depression is a feature of deficiencies of folic acid, vitamin B 2 (riboflavin) and vitamin B 6 (pyridoxine), while vitamin B 1 (thiamine) deficiency is associated with several psychosyndromes including alcoholism and schizophrenia. Data

from recent studies of vitamin deficiency reveal that gross manifestations such as beri-beri (characteristics include Wernicke's encephalopathy and Korsakoff's syndrome) and pellagra (characteristics include fatigue, insomnia and encephalopathy) are now relatively rare in the Western world. However, milder and subclinical syndromes are still common. For example, the prevalence of low levels of vitamin B 12 (cyanocobalamin) is has been estimated to be 5.8 to 26.1% in psychiatric patients, while that of folic acid is higher at 15 to 51% (derived from various studies). Despite these apparent associations, whether deficiencies of vitamins are causal in neuropsychiatric disorders or a result of them is difficult to determine. For example, there is little direct evidence of a causal role for folic acid in neuropsychiatric disorders, except in the rare in-born errors of metabolism that present with neuropsychiatric abnormalities. It is known that folic acid deficiency is associated with the use of many therapeutic drugs, concomitant physical illnesses and chronicity of psychiatric illness. However, retrospective studies of the effects of folic acid replacement therapy in deficient patients, employing clinical and social outcome criteria, have shown an improvement in psychiatric symptoms over a period of 6 to 12 months in most patients. Controlled studies of folic acid replacement therapy are also encouraging. In 1 double-blind, placebo-controlled add-on trial involving patients with endogenous depression and schizophrenia, the majority of folic acid treated patients improved compared with placebo recipients. The situation with regard to a causal role for other vitamins in neuropsychiatric disorders is even less clear. Obviously, more data are needed in this area to assist clinicians in determining the aetiology of episodes of depression and other neuropsychiatric disorders and, ultimately, their treatment.

Red cell folate concentrations in psychiatric patients

Carney M.W.P.; Chary T.K.N.; Laundy M.; Bottiglieri T.; Chanarin I.; Reynolds E.H.; Toone B. Department of Psychiatry, Clinical Research Centre, Northwick Park Hospital, Watford Road,Harrow HA1 3UJ United Kingdom

Journal of Affective Disorders (J. AFFECT. DISORD.) (Netherlands) 1990, 19/3 (207-213) Red cell folate and vitamin B12 estimations were performed on 243 successively admitted in-patients at a District General Hospital Psychiatric Unit and 42 out-patients (29 attending a lithium clinic). Patients were classified into five diagnostic groups. The mean ages of the manic and schizophrenic patients were lower than of the depressed or euthymic patients but age was not correlated with red cell folate or serum B12 levels in any group. There were 89 (31%) patients with red cell folate below 200 ng/ml and 35 (12%) with concentrations below 150 ng/ml. Significantly more of these low-folate patients were in-patients than outpatients. The mean red cell folate in the depressed patients was significantly lower than in the euthymic, manic and schizophrenic groups. Alcoholics had a similar mean red cell folate to depressed patients which was not quite significantly lower than the other groups. The mean serum B12 level in the alcoholics was, however, significantly raised. There were no significant differences in red cell folate or serum B12 between lithium-treated and untreated euthymic patients. The highest proportions of values below 200 ng/ml and 150 ng/ml were found in depressed and alcoholic patients. Endogenous depressives had the highest percentage of values below 150 ng/ml (folate-deficient) of all

psychiatric groups and alcoholic patients. The significance of these findings is discussed.

A controlled clinical trial of L-tryptophan in acute mania.

Chouinard G, Young SN, Annable L.

Biol Psychiatry 1985 May;20(5):546-57

In a 2-week study, 24 newly admitted manic patients were treated for 1 week with L-tryptophan (12 g/day); during the second week, half the patients, chosen at random, continued to receive tryptophan, while placebo was substituted in the other half under double-blind conditions. In the open phase of the study, there was a clinically and statistically (p less than 0.001) significant reduction in manic symptom scores, with little need for haloperidol prn. Patients who continued to be treated with tryptophan showed no significant change in mean scores during the second week, but those who were switched to placebo tended (p less than 0.10) to show an increase in the mean scores for manic symptoms. There was a significant (p less than 0.05) increase in the geometric mean of morning fasting total and free plasma tryptophan concentrations in men, but not in women. These results suggest that increasing the synthesis of 5-hydroxytryptamine has some therapeutic effect in mania.

Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial.

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J Affect Disord 2000 Nov;60(2):121-30

BACKGROUND: A consistent finding in major depression has been a low plasma and red cell folate which has also been linked to poor response to antidepressants. The present investigation was designed to investigate whether the co-administration of folic acid would enhance the antidepressant action of fluoxetine.

METHODS: 127 patients were randomly assigned to receive either 500 microg folic acid or an identical looking placebo in addition to 20 mg fluoxetine daily. All patients met the DSM-III-R criteria for major depression and had a baseline Hamilton Rating Scale (17 item version) score for depression of 20 or more. Baseline and 10-week estimations of plasma folate and homocysteine were carried out.

RESULTS: Patients receiving folate showed a significant increase in plasma folate.This was less in men than in women. Plasma homocysteine was significantly decreased in women by 20.6%, but there was no significant change in men. Overall there was a significantly greater improvement in the fluoxetine plus folic acid group. This was confined to women where the mean Hamilton

Rating Scale score on completion was 6.8 (S.D. 4. 1) in the fluoxetine plus folate group, as compared to 11.7 (S.D. 6. 7) in the fluoxetine plus placebo group (< 0.001).A percentage of 93. 9 of women, who received the folic acid supplement, showed a good response (< 50% reduction in score) as compared to 61.1% of women who received placebo supplement (< 0.005). Eight (12.9%) patients in the fluoxetine plus folic acid group reported symptoms possibly or probably related to medication, whereas in the fluoxetine plus placebo group 19 (29.7%) patients reported such symptoms (< 0.05).

LIMITATIONS AND CONCLUSIONS: Folic acid is a simple method of greatly improving the antidepressant action of fluoxetine and probably other antidepressants. Folic acid should be given in doses sufficient to decrease plasma homocysteine. Men require a higher dose of folic acid to achieve this than women, but more work is required to ascertain the optimum dose of folic acid.

S-Adenosyl-Methionine improves depression in patients with Parkinson's disease in an open-label clinical trial.

Di Rocco A, Rogers JD, Brown R, Werner P, Bottiglieri T.

Department of Neurology, Beth Israel Medical Center-Albert Einstein College of Medicine, New York, NY 10003, USA.

Mov Disord 2000 Nov;15(6):1225-9

We report a pilot study of S-adenosyl-methionine (SAM) in 13 depressed patients with Parkinson's disease. All patients had been previously treated with other antidepressant agents and had no significant benefit or had intolerable side effects. SAM was administered in doses of 800 to 3600 mg per day for a period of 10 weeks. Eleven patients completed the study, and 10 had at least a 50% improvement on the 17-point Hamilton Depression Scale (HDS). One patient did not improve. Two patients prematurely terminated participation in the study because of increased anxiety. One patient experienced mild nausea, and another two patients developed mild diarrhea, which resolved spontaneously. The mean HDS score before treatment was 27.09 +/- 6.04 (mean +/- standard deviation) and was 9.55 +/- 7.29 after SAM treatment (< 0.0001). Although uncontrolled and preliminary, this study suggests that SAM is well tolerated and may be a safe and effective alternative to the antidepressant agents currently used in patients with Parkinson's disease.

Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients.

Edwards R, Peet M, Shay J, Horrobin D. University Department of Psychiatry, University of Sheffield, UK.

J Affect Disord 1998 Mar;48(2-3):149-55

BACKGROUND: There is a hypothesis that lack of n-3 polyunsaturated fatty acids (PUFAs) is of aetiological importance in depression. Docosahexaenoic acid, a member of the n-3 PUFA family, is a crucial component of synaptic cell membranes. The aim of this study was to measure RBC membrane fatty acids in a group of depressed patients relative to a well matched healthy control group. METHOD: Red blood cell (RBC) membrane levels, and dietary PUFA intake were measured in 10 depressed patients and 14 matched healthy control subjects. RESULTS: There was a significant depletion of RBC membrane n-3 PUFAs in the depressed subjects which was not due to reduced calorie intake. Severity of depression correlated negatively with RBC membrane levels and with dietary intake of n-3 PUFAs. CONCLUSION: Lower RBC membrane n-3 PUFAs are associated with the severity of depression. LIMITATIONS: Although patient numbers were small, confounding factors were well controlled for and the results were highly significant. Results of the dietary data would tend to be weakened due to the limitations associated with dietary assessment. CLINICAL RELEVANCE: The findings raise the possibility that depressive symptoms may be alleviated by n-3 PUFA supplementation.

Effect of vitamin B complex on neurotransmission and neurite outgrowth.

Fujii A, Matsumoto H, Yamamoto H. Department of Pharmacology, Nihon University School of Dentistry at Matsudo, Chiba, Japan.

Gen Pharmacol 1996 Sep;27(6):995-1000

1. The effect of vitamin B complex (vitamin B1, B6 and B12) was studied on nerve conduction velocity in acrylamide-neuropathy rats maintained on refined semisynthetic complete vitamin and vitamin B-deficient diets in vivo and on neurite outgrowth in vitro using cells obtained from dorsal root ganglions of mice. 2. Acrylamide neuropathy was clearer in the group maintained on a refined semisynthetic vitamin B-deficient diet than in those on a refined semisynthetic complete vitamin diet. The neurotoxicity was lowest in the group given vitamin B complex prophylactic-therapeutically, next higher following therapeutic administration and last with no vitamin B complex administration in both groups maintained on a refined semisynthetic vitamin B-deficient diet and a refined semisynthetic complete vitamin diet. 3. The nerve conduction velocity tended to decrease by treatment with acrylamide. The decrement of nerve conduction velocity was partially inhibited by vitamin B complex. No significant difference was found in the groups treated with acrylamide and given vitamin B complex prophylactic-therapeutically and the control (no acrylamide treatment) in the group maintained on a refined semisynthetic vitamin B-deficient diet. 4. The greatest neurite outgrowth was found in the group treated with vitamins B1, B6 and B12-enriched medium, followed by the group of vitamin B12-enriched and vitamin B1-enriched media. All groups treated with a vitamin B-enriched medium had significantly greater (< 0.01) outgrowth than the controls.

St John's wort for depression: a systematic review.

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Arch Intern Med 2000 Jan 24;160(2):152-6

To address whether St John's wort is useful for the treatment of depression we attempted to retrieve all English-language articles with data on the efficacy, safety, and availability of St John's wort. Randomized, controlled, double-blind trials were selected and assessed for methodological quality using a standardized checklist, and data on pharmacology, cost, regulation, and safety were extracted. Eight studies were identified, found to be of generally good methodological quality, and determined to provide a modest amount of data to suggest that St John's wort is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with the use of St John's wort ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. More data are required to assess both its use in severe depression and its efficacy compared with other antidepressants. Rates of side effects were low. As a dietary supplement, St John's wort is currently largely unregulated, but the Food and Drug Administration is reviewing plans to tighten its regulatory oversight.

St. John's Wort extract: efficacy for menopausal symptoms of psychological origin.

Grube B, Walper A, Wheatley D. Lichtwer Pharma AG, Berlin, Germany.

Adv Ther 1999 Jul-Aug;16(4):177-86

Herbal remedies such as St. John's Wort preparations can be used successfully to relieve the psychological and vegetative symptoms of menopause. This drug-monitoring study investigated 12 weeks of treatment with St. John's Wort, one tablet three times daily (900 mg Hypericum, Kira), in 111 women from a general medical practice. The patients, who were between 43 and 65 years old, had climacteric symptoms characteristic of the pre- and postmenopausal state. Treatment outcome was evaluated by the Menopause Rating Scale, a self-designed questionnaire for assessing sexuality, and the Clinical Global Impression scale. The incidence and severity of typical psychological, psychosomatic, and vasomotor symptoms were recorded at baseline and after 5, 8, and 12 weeks of treatment. Substantial improvement in psychological and psychosomatic symptoms was observed. Climacteric complaints diminished or disappeared completely in the majority of women (76.4% by patient evaluation and 79.2% by physician evaluation). Of note, sexual well-being also improved after treatment with St. John's Wort extract.

Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine.

Harrer G, Schmidt U, Kuhn U, Biller A. Institut fur Forensische Psychiatrie der Universitat Salzburg, Germany.

Arzneimittelforschung 1999 Apr;49(4):289-96

In a randomised double-blind comparative trial, the antidepressant efficacy of a daily dose of 800 mg of the St. John's wort extract LoHyp-57 (dry extract of St. John's wort, drug extrakt ratio 5-7:1, solvent, ethanol 60% [w/w]) was shown to be equivalent to that of 20 mg fluoxetine (CAS 54910-89-3) in elderly patients with mild or moderate depressive episodes according to ICD 10 (International Statistical Classification of Diseases and Related Health Problems). Treatment was given for six weeks. 149 out-patients (129 females and 20 males) were included in the intention-to-treat analysis. 72 of these patients were assigned to the ICD 10 diagnostic criterion F32.0 (mild depressive episode), while 77 patients were suffering from moderate depressive episodes, corresponding to F32.1. The principal target criterion was the patient's global score on the HAMILTON Depression Scale (items 1-17). During the six-week course of treatment with LoHyp-57, the HAMILTON global score fell from 16.60 points at entry to 7.91 points, and in the fluoxetine sample it fell from 17.18 to 8.11 points. In the group of patients with mild depressive episodes, the score showed a mean fall from 14.21 to 6.21 points on LoHyp-57, and from 15.21 to 7.46 points on fluoxetine. In patients with moderate depressive episodes, the score showed a mean fall from 18.73 to 9.43 points on LoHyp-57 and from 19.10 to 8.75 points on fluoxetine. The efficacy of both medications was found to be equivalent both in mild and moderate depressive episodes. Both treatment groups showed adverse drug reactions (ADRs). Twelve ADRs with a possible relationship to the study medication were reported during treatment with LoHyp-57. Six patients were prematurely withdrawn from treatment with the study medication for this reason. On fluoxetine 17 ADRs occurred with a possible relationship to the study medication. These led to abandonment of treatment and therefore premature withdrawal from the study in 8 cases.

Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy.

Hibbeln JR, Salem N Jr. Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA.

Am J Clin Nutr 1995 Jul;62(1):1-9

Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n-6 and n-3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n-3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and post-partum depression. We postulate that

adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n-3 polyunsaturated fatty acids may reduce coronary artery disease.

Decreased cerebral 5-HT1A receptors during ageing: reversal by Ginkgo biloba extract (EGb 761).

Huguet F, Drieu K, Piriou A. Institut des Xenobiotiques, Faculte de Medecine et de Pharmacie, Poitiers, France.

J Pharm Pharmacol 1994 Apr;46(4):316-8

Investigation of [3H]8-hydroxy-2(di-n-propylamino)tetralin binding to 5-HT1A receptors in cerebral cortex membranes of Wistar rats showed that the maximal number of binding sites (Bmax) was reduced significantly (22%) in aged (24-month-old) as compared with young (4-month-old) animals. Chronic treatment with Ginkgo biloba extract did not alter binding in young rats but increased binding density significantly (33%) in aged rats. These results confirm previously described age-related 5-hydroxytryptaminergic alterations. Together with data in the literature, they also suggest a restorative effect in aged rats, associated with decreased receptor density resulting from the protective action of Ginkgo biloba extract treatment on neuronal membrane.

Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial.

Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, Herbert J, Chatterjee VK. Department of Endocrinology, University of Oxford, Radcliffe Infirmary, Oxford, United Kingdom.

J Clin Endocrinol Metab 2000 Dec;85(12):4650-6

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are adrenal precursors of steroid biosynthesis and centrally acting neurosteroids. Glucocorticoid and ineralocorticoid deficiencies in Addison's disease require life-long hormone replacement, but the associated failure of DHEA synthesis is not corrected. We conducted a randomized, double blind study in which 39 patients with Addison's disease received either 50 mg oral DHEA daily for 12 weeks, followed by a 4-week washout period, then 12 weeks of placebo, or vice versa. After DHEA treatment, levels of DHEAS and Delta(4)-androstenedione rose from subnormal to within the adult physiological range. Total testosterone increased from subnormal to low normal with a fall in serum sex hormone-binding globulin in females, but with no change in either parameter in males. In both sexes, psychological assessment showed significant enhancement of self-esteem with a tendency for improved overall well-being. Mood and fatigue also improved significantly, with benefit being evident in the evenings. No effects on cognitive or sexual function, body composition, lipids, or bone mineral density were observed. Our results indicate that DHEA replacement corrects this steroid deficiency effectively and improves some aspects of psychological function.

Beneficial effects in males, independent of circulating testosterone levels, suggest that it may act directly on the central nervous system rather than by augmenting peripheral androgen biosynthesis. These positive effects, in the absence of significant adverse events, suggest a role for DHEA replacement therapy in the treatment of Addison's disease.

Effect of acute and chronic administration of dehydroepiandrosterone on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane-induced wet dog shaking behavior in rats.

Inagaki M, Kagaya A, Takebayashi M, Horiguchi J, Yamawaki S. Department of Psychiatry and Neurosciences, Hiroshima University School of Medicine, Japan.

J Neural Transm 1999;106(1):23-33

It has been reported that dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEA-S) is associated with affective disorders and that pathology of affective disorders are related with dysfunction of serotonin(5-HT)-2A receptor-mediated responses. In this study, we investigated the effect of DHEA on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2 aminopropane (DOI), 5-HT-2A receptor agonist, -induced wet dog shaking behavior (WDS) in rats. Acute treatment with DHEA inhibited the DOI-induced WDSs dose dependently. This inhibition was recovered by opioid receptor antagonist, naltrexone. 5-HT-2A receptor-mediated WDSs were desensitized after chronic treatment with DOI, however chronic treatment with DHEA had no effect on this desensitization. Chronic treatment with DHEA had no facilitating effect of chronic dexamethasone treatment on DOI-induced WDSs. These findings may lead the possibility that DHEA has the inhibitory effect of 5-HT-2A mediated signaling pathway via non-genomic action.

Treatment of seasonal affective disorder (SAD) with hypericum extract.

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Pharmacopsychiatry 1997 Sep;30 Suppl 2:89-93

Seasonal affective disorder (SAD) is a subgroup of major depression and characterized by a regular occurrence of symptoms in autumn/winter and full remission or hypomania in spring/summer. Light therapy (LT) and recently pharmacotherapy with specific antidepressants have been shown to be beneficial. Within the array of pharmacotherapy hypericum extract has also been found to be effective in a single-blind study (Martinez et al., 1994). In this 4 weeks treatment study 900 mg of hypericum was associated with a significant reduction in the total score of the Hamilton Depression Rating Scale. There was no significant difference when bright light therapy was combined with hypericum, compared to the situation without bright light therapy. Overall, hypericum was well tolerated and therefore the data suggest that pharmacological treatment with hypericum may be an efficient therapy in patients with SAD, which needs to be substantiated in further controlled studies.

Folates: supplemental forms and therapeutic applications.

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Altern Med Rev 1998 Jun;3(3):208-20

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides form purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine. Oral folates are generally available in two supplemental forms, folic and folinic acid. Administration of folinic acid bypasses the deconjugation and reduction steps required for folic acid. Folinic acid also appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect. Therapeutically, folic acid can reduce homocysteine levels and the occurrence of neural tube defects, might play a role in preventing cervical dysplasia and protecting against neoplasia in ulcerative colitis, appears to be a rational aspect of a nutritional protocol to treat vitiligo, and can increase the resistance of the gingiva to local irritants, leading to a reduction in inflammation. Reports also indicate that neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome.

Vitamin D3 enhances mood in healthy subjects during winter.

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Psychopharmacology (Berl) 1998 Feb;135(4):319-23

Mood changes synchronised to the seasons exist on a continuum between individuals, with anxiety and depression increasing during the winter months. An extreme form of seasonality is manifested as the clinical syndrome of seasonal affective disorder (SAD) with carbohydrate craving, hypersomnia, lethargy, and changes in circadian rhythms also evident. It has been suggested that seasonality and the symptoms of SAD may be due to changing levels of vitamin D3, the hormone of sunlight, leading to changes in brain serotonin. Forty-four healthy subjects were given 400 IU, 800 IU, or no vitamin D3 for 5 days during late winter in a random double-blind study. Results on a self-report measure showed that vitamin D3 significantly enhanced positive affect and there was some evidence of a reduction in negative affect. Results are discussed in terms of their implications for seasonality, SAD, serotonin, food preference, sleep, and circadian rhythms.

Controlled trials of inositol in psychiatry.

Levine J. Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel.

Eur Neuropsychopharmacol 1997 May;7(2):147-55

Inositol is a simple polyol precursor in a second messenger system important in the brain. Cerebrospinal fluid inositol has been reported as decreased in depression. A double-blind controlled trial of 12 g daily of inositol in 28 depressed patients for four weeks was performed. Significant overall benefit for inositol compared to placebo was found at week 4 on the Hamilton Depression Scale. No changes were noted in hematology, kidney or liver function. Since many antidepressants are effective in panic disorder, twenty-one patients with panic disorder with or without agoraphobia completed a double-blind, placebo-controlled, four week, random-assignment crossover treatment trial of inositol 12 g per day. Frequency and severity of panic attacks and severity of agoraphobia declined significantly with inositol compared to placebo. Side-effects were minimal. Since serotonin re-uptake inhibitors benefit obsessive compulsive disorder (OCD) and inositol is reported to reverse desensitization of serotonin receptors, thirteen patients with OCD completed a double-blind controlled crossover trial of 18 g inositol or placebo for six weeks each. Inositol significantly reduced scores of OCD symptoms compared with placebo. A controlled double-blind crossover trial of 12 g daily of inositol for a month in twelve anergic schizophrenic patients, did not show any beneficial effects. A double-blind controlled crossover trial of 6 g of inositol daily vs. glucose for one month each was carried out in eleven Alzheimer patients, with on clearly significant therapeutic effects. Antidepressant drugs have been reported to improve attention deficit disorder (ADDH) with hyperactivity symptomatology. We studied oral inositol in children with ADDH in a double-blind, crossover, placebo-controlled manner. Eleven children, mean age 8.9 +/- 3.6 years were enrolled in an eight week trial of inositol or placebo at a dose of 200 mg/kg body weight. Results show a trend for aggravation of the syndrome with myo-inositol as compared to placebo. Recent studies suggest that serotonin re-uptake inhibitors are helpful in at least some symptoms of autism. However a controlled double-blind crossover trial of inositol 200 mg/kg per day showed no benefit in nine children with autism. Cholinergic agonists have been reported to ameliorate electroconvulsive therapy (ECT)-induced memory impairment. Inositol metabolism is involved in the second messenger system for several muscarinic cholinergic receptors. Inositol 6 g daily was given in a crossover-double-blind manner for five days before the fifth or sixth ECT to a series of twelve patients, without effect. These results suggest that inositol has therapeutic effects in the spectrum of illness responsive to serotonin selective re-uptake inhibitors, including depression, panic and OCD, and is not beneficial in schizophrenia, Alzheimer's ADDH, autism or ECT-induced cognitive impairment.

Double-blind, controlled trial of inositol treatment of depression.

Levine J, Barak Y, Gonzalves M, Szor H, Elizur A, Kofman O, Belmaker RH. Yehuda Abarbanel Mental Health Center, Bat Yam, Israel.

Am J Psychiatry 1995 May;152(5):792-4

OBJECTIVE: CSF levels of inositol have been reported to be lower than normal in depressed subjects. The authors administered inositol to depressed patients in a double-blind, controlled trial. METHOD: Under double-blind conditions, 12 g/day of inositol (N = 13) or placebo (N = 15) was administered to depressed patients for 4 weeks. RESULTS: The overall improvement in scores on the Hamilton Depression Rating Scale was significantly greater for inositol than for placebo at week 4. No changes were noted in hematology or in kidney or liver function. CONCLUSIONS: This may be the first use of the precursor strategy for a second messenger rather than a neurotransmitter in treating depression. Although inositol had a significant antidepressant effect in this study, replication is crucial.

Follow-up and relapse analysis of an inositol study of depression.

Levine J, Barak Y, Kofman O, Belmaker RH. Abarbanel Mental Health Center, Bat Yam, Israel.

Isr J Psychiatry Relat Sci 1995;32(1):14-21

A recent controlled double-blind study of 28 patients treated with 12 gm daily of inositol or placebo revealed significant antidepressant effect for this second messenger precursor. Patients were followed-up by interview and Hamilton Depression Scale 10-12 months after the end of the study. Half of the patients who had responded well to inositol relapsed rapidly after inositol discontinuation whereas none of those who responded to placebo relapsed rapidly after placebo cessation. Klein suggested that true drug responders to tricyclic antidepressants respond slowly and gradually whereas placebo responders improve early in an abrupt fashion. However, in the recent study both inositol and placebo responders improved at similar rates. Hamilton Depression Scale Scores 10-12 months after completion of the study were not significantly different between those who had responded and those who had not responded to inositol or to placebo.

St John's wort for depression--an overview and meta-analysis of randomised clinical trials.

Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. Projekt Munchener Modell, Ludwig-Maximilians-Universitat, Munich, Germany.

BMJ 1996 Aug 3;313(7052):253-8

OBJECTIVE--To investigate if extracts of Hypericum perforatum (St John's wort) are more effective than placebo in the treatment of depression, are as effective as standard antidepressive treatment, and have fewer side effects than standard antidepressant drugs. DESIGN-Systematic review and meta-analysis of trials revealed by searches. TRIALS--23 randomised trials including a total of 1757 outpatients with mainly mild or moderately severe depressive disorders: 15 (14 testing single preparations and one a combination with other plant extracts) were placebo controlled, and eight (six testing single preparations and two combinations) compared hypericum with another drug treatment. MAIN

OUTCOME MEASURES--A pooled estimate of the responder rate ratio (responder rate in treatment group/responder rate in control group), and numbers of patients reporting and dropping out for side effects. RESULTS--Hypericum extracts were significantly superior to placebo (ratio = 2.67; 95% confidence interval 1.78 to 4.01) and similarly effective as standard antidepressants (single preparations 1.10; 0.93 to 1.31, combinations 1.52; 0.78 to 2.94). There were two (0.8%) drop outs for side effects with hypericum and seven (3.0%) with standard antidepressant drugs. Side effects occurred in 50 (19.8%) patients on hypericum and 84 (52.8%) patients on standard antidepressants. CONCLUSION--There is evidence that extracts of hypericum are more effective than placebo for the treatment of mild to moderately severe depressive disorders. Further studies comparing extracts with standard antidepressants in well defined groups of patients and comparing different extracts and doses are needed.

Can winter depression be prevented by Ginkgo biloba extract? A placebo-controlled trial.

Lingaerde O, Foreland AR, Magnusson A. Department of Research and Education, Aker Hospital, Oslo, Norway.

Acta Psychiatr Scand 1999 Jul;100(1):62-6

OBJECTIVE: The aim was to test the hypothesis that the Ginkgo biloba extract PN246, in tablet form (brand name Bio-Biloba), may prevent the symptoms of winter depression (WD) in patients with seasonal affective disorder (SAD). METHOD: A total of 27 SAD patients were randomized to receive double-blind placebo or Bio-Biloba for 10 weeks or until they developed symptoms of WD, starting in a symptom-free phase about 1 month before expected WD symptoms. An extended Montgomery-Asberg Depression Rating Scale was completed before and immediately after termination of medication. The patients also self-rated some key symptoms on a visual analogue scale every 2 weeks during the trial. RESULTS: There were no significant differences between the treatment groups in the number of patients who developed treatment-requiring WD, or in the development of single key symptoms during the trial. CONCLUSION: We did not find that Ginkgo biloba was able to prevent the development of the symptoms of winter depression.

Effect of St. John's wort (Hypericum perforatum) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers.

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Life Sci 2000 Jan 21;66(9):PL133-9

The effects of the herb St. John's wort (Hypericum perforatum), a purported antidepressant, on the activity of cytochrome P-450 (CYP) 2D6 and 3A4 was assessed in seven normal volunteers. Probe substrates dextromethorphan (2D6

activity) and alprazolam (3A4 activity) were administered orally with and without the co-administration of St. John's wort. Urinary concentrations of dextromethorphan and dextrorphan were quantified and dextromethorphan metabolic ratios (DMRs) determined. Plasma samples were collected (0-60 hrs) for alprazolam pharmacokinetic analysis sufficient to estimate tmax, Cmax, t 1/2, and AUC. Validated HPLC methods were used to quantify all compounds of interest. No statistically significant differences were found in any estimated pharmacokinetic parameter for alprazolam or DMRs. These results suggest that St. John's wort, when taken at recommended doses for depression, is unlikely to inhibit CYP 2D6 or CYP 3A4 activity.

EGG phosphatidylcholine combined with vitamin B12 improved memory impairment following lesioning of nucleus basalis in rats.

Masuda Y, Kokubu T, Yamashita M, Ikeda H, Inoue S. Q.P. Corporation, Department of Neuropsychiatry, Kochi Medical School, Tokyo, Japan.

Life Sci 1998;62(9):813-22

We investigated the effects of egg phosphatidylcholine (PC) combined with vitamin B12 on memory in the Morris water maze task, and on choline and acetylcholine (ACh) concentrations in the brain of rats. Animals with nucleus basalis Magnocellularis (NBM) lesion received intragastric administration of egg PC or vitamin B12, or both for 18 days. Memory acquisition and retention were remarkably impaired in NBM lesioned rats compared with in sham-operated control. NBM lesioned group had lower choline and ACh concentrations than control group in the frontal cortex. High dose of egg PC alone significantly increased choline concentration, but did not change ACh concentration in the frontal cortex. High dose of vitamin B12 alone did not change choline and ACh concentrations in the brain. Either egg PC or vitamin B12 did not improve memory acquisition and retention. However, low dose of egg PC combined with vitamin B12 significantly increased ACh concentration and improved memory acquisition and retention in the NBM lesioned rats. We concluded that egg PC combined with vitamin B12 improved the memory impairment of NBM lesioned rats through the action on the cholinergic neurons.

Evaluation of the relative potency of individual competing amino acids to tryptophan transport in endogenously depressed patients.

Moller, Svend E.

Psychiatry Research 3(2):141-150, 1980

The relative potency of the individual amino acids as competitive inhibitors of tryptophan transport into the human brain was evaluated retrospectively; the combination of competitors that yields the highest predictive value of the plasma tryptophan ratio for the course of treatment of depressed patients with L-tryptophan was also examined. Phenylalanine consistently reduced, and isoleucine slightly reduced the predictive value of the plasma tryptophan ratio. The ratio of

tryptophan to the sum of valine, leucine, and tyrosine was identified as most predictive for the therapeutic response to tryptophan. L-tryptophan responders showed a normal plasma total tryptophan concentration as did the nonresponders, whereas the concentration of the three competitors was significantly elevated. It is concluded that while the plasma ratio of tryptophan to the sum of valine, leucine, and tyrosine is a useful predictor of the course of depressives on L-tryptophan, it does not definitely separate out the L-tryptophan responders from the control subjects.

Relationship between plasma ratio of tryptophan to competing amino acids and the response to L-tryptophan treatment in endogenously depressed patients.

Moller SE, Kirk L, Honore P.

J Affect Disord 1980 Mar;2(1):47-59

The ratio of the plasma of total tryptophan to those amino acids that compete with tryptophan during transport into the brain was determined in 60 control subjects and 87 patients suffering from endogenous depression, all females. The plasma ratio in the control subjects showed a significant negative correlation with age. There was no significant difference in the distribution of the biochemical data between the control subjects and the depressed patients. There was a significant higher proportion of bipolar depressed subjects compared to unipolar depressives and patients of uncertain polarity who showed a plasma ratio in the lower normal range. Thirty-two patients were subsequently treated with L-tryptophan. In the patients who showed a particularly low plasma ratio of tryptophan to competing amino acids a remission frequency of 80% was observed on day 14. The efficacy of L-tryptophan in the patients who showed a plasma ratio within the upper normal range was extremely poor. The results suggest that the ratio in the plasma of tryptophan to competing amino acids is a useful predictor of the course of treatment of depressed subjects with L-tryptophan.

St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor.

Moore LB, Goodwin B, Jones SA, Wisely GB, Serabjit-Singh CJ, Willson TM, Collins JL, Kliewer SA. Department of Molecular Endocrinology, Glaxo Wellcome Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709, USA.

Proc Natl Acad Sci U S A 2000 Jun 20;97(13):7500-2

St. John's wort (Hypericum perforatum) is an herbal remedy used widely for the treatment of depression. Recent clinical studies demonstrate that hypericum extracts increase the metabolism of various drugs, including combined oral contraceptives, cyclosporin, and indinavir. In this report, we show that hyperforin, a constituent of St. John's wort with antidepressant activity, is a potent ligand (K(i) = 27 nM) for the pregnane X receptor, an orphan nuclear receptor that

regulates expression of the cytochrome P450 (CYP) 3A4 monooxygenase. Treatment of primary human hepatocytes with hypericum extracts or hyperforin results in a marked induction of CYP3A4 expression. Because CYP3A4 is involved in the oxidative metabolism of >50% of all drugs, our findings provide a molecular mechanism for the interaction of St. John's wort with drugs and suggest that hypericum extracts are likely to interact with many more drugs than previously had been realized.

The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women.

Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. Department of Reproductive Medicine, School of Medicine, University of California San Diego, La Jolla, USA.

Clin Endocrinol (Oxf) 1998 Oct;49(4):421-32

OBJECTIVE: The biological role of the adrenal sex steroid precursors--DHEA and DHEA sulphate (DS) and their decline with ageing remains undefined. We observed previously that administration of a 50 daily dose of DHEA for 3 months to age-advanced men and women resulted in an elevation (10%) of serum levels of insulin-like growth factor-I (IGF-I) accompanied by improvement of self-reported physical and psychological well-being. These findings led us to assess the effect of a larger dose (100 mg) of DHEA for a longer duration (6 months) on circulating sex steroids, body composition (DEXA) and muscle strength (MedX).

SUBJECTS AND DESIGN: Healthy non-obese age-advanced (50-65 yrs of age) men (n = 9) and women (n = 10) were randomized into a double-blind placebo-controlled cross-over trial. Sixteen subjects completed the one-year study of six months of placebo and six months of 100 mg oral DHEA daily.

MEASUREMENTS: Fasting early morning blood samples were obtained. Serum DHEA, DS, sex steroids, IGF-I, IGFBP-1, IGFBP-3, growth hormone binding protein (GHBP) levels and lipid profiles as well as body composition (by DEXA) and muscle strength (by MedX testing) were measured at baseline and after each treatment.

RESULTS: Basal serum levels of DHEA, DS, androsternedione (A), testosterone (T) and dihydrotestosterone (DHT) were at or below the lower range of young adult levels. In both sexes, a 100 mg daily dose of DHEA restored serum DHEA levels to those of young adults and serum DS to levels at or slightly above the young adult range. Serum cortisol levels were unaltered, consequently the DS/cortisol ratio was increased to pubertal (10:1) levels. In women, but not in men, serum A, T and DHT were increased to levels above gender-specific young adult ranges. Basal SHBG levels were in the normal range for men and elevated in women, of whom 7 of 8 were on oestrogen replacement therapy. While on DHEA, serum SHBG levels declined with a greater (P < 0.02) response in women (-40 +/- 8%; P = 0.002) than in men (-5 +/- 4%; P = 0.02). Relative to

baseline, DHEA administration resulted in an elevation of serum IGF-I levels in men (16 +/- 6%, P = 0.04) and in women (31 +/- 12%, P = 0.02). Serum levels of IGFBP-1 and IGFBP-3 were unaltered but GHBP levels declined in women (28 +/- 6%; P = 0.02) not in men. In men, but not in women, fat body mass decreased 1.0 +/- 0.4 kg (6.1 +/- 2.6%, P = 0.02) and knee muscle strength 15.0 +/- 3.3% (P = 0.02) as well as lumbar back strength 13.9 +/- 5.4% (P = 0.01) increased. In women, but not in men, an increase in total body mass of 1.4 +/- 0.4 kg (2.1 +/- 0.7%; P = 0.02) was noted. Neither gender had changes in basal metabolic rate, bone mineral density, urinary pyridinoline cross-links, fasting insulin, glucose, cortisol levels or lipid profiles. No significant adverse effects were observed.

CONCLUSIONS: A daily oral 100 mg dose of DHEA for 6 months resulted in elevation of circulating DHEA and DS concentrations and the DS/cortisol ratio. Biotransformation to potent androgens near and slightly above the range of their younger counterparts occurred in women with no detectable change in men. Given this hormonal milieu, an increase in serum IGF-I levels was observed in both genders but dimorphic responses were evident in fat body mass and muscle strength in favour of men. These differences in response to DHEA administration may reflect a gender specific response to DHEA and/or the presence of confounding factor(s) in women such as oestrogen replacement therapy.

Tryptophan depletion and risk of depression relapse: a prospective study of tryptophan depletion as a potential predictor of depressive episodes.

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Biol Psychiatry 2000 Aug 15;48(4):327-9

BACKGROUND: This study investigated the relationship between depressive symptom response during tryptophan depletion and future depressive episodes. METHODS: Twelve subjects with prior major depressive episodes in remission and medication-free for > or =3 months (patients), and 12 matched healthy (control) subjects received two tryptophan depletion tests 1 week apart. During follow-up the Hamilton Depression Rating Scale was administered weekly for 1 month, monthly for 3 months, and once at 6 and 12 months. RESULTS: With results from both tests, tryptophan depletion has a sensitivity of 78%, specificity of 80%, positive predictive value of 70%, and negative predictive value of 86% to identify future depressive episodes. Survival analysis shows that mood response to tryptophan depletion reliably predicts major depressive episodes during the follow-up year (r =.2725, p =.014). CONCLUSIONS: Tryptophan depletion may be clinically useful in identifying individuals at risk for future major depressive episodes.

Cognitive behavior therapy, relaxation training, and tricyclic antidepressant medication in the treatment of depression.

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Psychol Rep 1995 Oct;77(2):403-20

Outcomes of seven treatment trials comparing cognitive behavioral therapy to treatment with tricyclic antidepressant medication in major depressive disorder have been quite similar to one another. This led us to question whether treatment outcome in time-limited studies reflected a unique effect of cognitive behavioral therapy. To test the uniqueness hypothesis, relaxation training, a nonpharmacologic, noncognitive treatment, was chosen as a comparison for cognitive behavioral therapy as well as drug therapy. Treatment duration was 16 weeks. The sample of 37 patients treated for major depressive disorder was less depressed than those previously studied. For both cognitive behavioral therapy and relaxation training, outcome of depression was superior to that of tricyclic antidepressant medication by endpoint analysis. The posttreatment scores on the Beck Depression Inventory of 82% of the group receiving cognitive behavioral therapy improved to a Beck Depression Inventory score < or = 9 which was not significantly greater than that for the group receiving relaxation training (73%), so a unique effect was not demonstrated for cognitive behavioral therapy. The outcome for tricyclic antidepressant medication (29% improved to criteria) was significantly worse than that for cognitive behavioral therapy. The patient's pretreatment initial expectancy was not predictive.

[Neuropsychic effects of dehydroepiandrosterone]. [Article in French]

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Ann Med Interne (Paris) 2001 Apr;152 Suppl 3:43-9

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) are secreted primarily by the adrenal glands. DHEA could also be a neuroactive steroidal hormone. Because basal levels of DHEA and DHEA-S in humans decrease significantly with age, these hormones have been assumed to be involved in the aging process and in a number of pathologies which develop with aging: immunosenescence, increased mortality, increased incidence of cancer, osteoporosis and cardiovascular diseases. However, its role is still unknown. In humans, cross sectional and longitudinal studies have shown that DHEA might be associated with global measures of well-being and functioning, but positive effects on measures of memory and attention could not be found. Studies investigating DHEA and DHEA-S levels in dementia have produced controversial results. Short-term experimental studies have not shown significant improvement in global measures of well-being and functioning in healthy subjects but have revealed preliminary evidence for mood enhancing and antidepressant effects of DHEA. There is no evidence that DHEA could induce addiction in human beings.

Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women.

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Psychother Psychosom 1993;59(1):34-40

S-adenosyl-L-methionine (SAMe) is a naturally occurring substance which is a major source of methyl groups in the brain and has been found in previous studies to be an effective antidepressant. The aim of this study was to assess the efficacy of oral SAMe in the treatment of depressed postmenopausal women in a 30-day double-blind placebo-controlled randomized trial. During the course of the study, 80 women, between the ages of 45 and 59, who were diagnosed as having DSM-III-R major depressive disorder or dysthymia between 6 and 36 months following either natural menopause or hysterectomy, underwent 1 week of single-blind placebo washout, followed by 30 days of double-blind treatment with either SAMe 1,600 mg/day or placebo. There was a significantly greater improvement in depressive symptoms in the group treated with SAMe compared to the placebo group from day 10 of the study. Side effects were mild and transient.

Plasma vitamin C concentrations in patients in a psychiatric hospital.

Schorah CJ, Morgan DB, Hullin RP.

Hum Nutr Clin Nutr 1983 Dec;37(6):447-52

Plasma vitamin C was measured in 885 patients in a psychiatric hospital and in 110 healthy controls. The average value was lower in the patients (0.51 mg/100 ml) than in the controls (0.87 mg/100 ml). Length of stay in hospital had little effect on plasma vitamin C in the patients, but the values were marginally lower in males, females on iron therapy and in those with senile dementia. In the patients, many of whom had been offered a similar diet for several years, age was not associated with a change in plasma vitamin C and this suggests that changes in vitamin C with age that have been reported reflect differences in intake. Few patients had values as low as those found in clinical scurvy (less than 0.1 mg/100 ml), but many (32 per cent) had concentrations below the threshold (0.35 mg/100 ml) at which some detrimental effects on health have been reported.

Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression.

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Int Clin Psychopharmacol 2000 Mar;15(2):61-8

Treatment with St John's wort extract tablets (hypericum Ze 117) and the commonly used slow serotonin reuptake inhibitor (SSRI) fluoxetine was

compared in patients with mild-moderate depression with entry Hamilton Depression Scale (HAM-D) (21-item) in the range 16-24, in a randomized, double-blind, parallel group comparison in 240 subjects; fluoxetine: 114 (48%), hypericum: 126 (52%). After 6 weeks' treatment, mean HAM-D at endpoint decreased to 11.54 on hypericum and to 12.20 on fluoxetine (P < 0.09), while mean Clinical Global Impression (CGI) item I (severity) was significantly (P < 0.03) superior on hypericum, as was the responder rate (P = 0.005). Hypericum safety was substantially superior to fluoxetine, with the incidence of adverse events being 23% on fluoxetine and 8% on hypericum. The commonest events on fluoxetine were agitation (8%), GI disturbances (6%), retching (4%), dizziness (4%), tiredness, anxiety/nervousness and erectile dysfunction (3% each), while on hypericum only GI disturbances (5%) had an incidence greater than 2%. We concluded that hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although hypericum may be superior in improving the responder rate, the main difference between the two treatments is safety. Hypericum was superior to fluoxetine in overall incidence of side-effects, number of patients with side-effects and the type of side-effect reported.

Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial.

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Arch Gen Psychiatry 1999 May;56(5):407-12

BACKGROUND: Omega3 fatty acids may inhibit neuronal signal transduction pathways in a manner similar to that of lithium carbonate and valproate, 2 effective treatments for bipolar disorder. The present study was performed to examine whether omega3 fatty acids also exhibit mood-stabilizing properties in bipolar disorder. METHODS: A 4-month, double-blind, placebo-controlled study, comparing omega3 fatty acids (9.6 g/d) vs placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder. RESULTS: A Kaplan-Meier survival analysis of the cohort found that the omega3 fatty acid patient group had a significantly longer period of remission than the placebo group (P = .002; Mantel-Cox). In addition, for nearly every other outcome measure, the omega3 fatty acid group performed better than the placebo group. CONCLUSION: Omega3 fatty acids were well tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder.

Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes.

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Int J Gynaecol Obstet 1999 Dec;67(3):169-74

OBJECTIVE: To evaluate the degree of psychological dysfunction and levels of stress hormones in postmenopausal women with climacteric syndromes and effect of Korean red ginseng (RG) on them. METHODS: ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g RG. Blood samples were collected in the early morning on the bed-rest. In postmenopausal women with climacteric syndromes such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment with RG. RESULTS: CMI score as well as anxiety (A)-state in STAI score in postmenopausal women with climacteric syndromes was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndromes were about a half of those without climacteric syndrome. Consequently, cortisol/DHEA-S (C/D) ratio was significantly higher in postmenopausal women with climacteric syndromes than in those without climacteric syndrome. When postmenopausal women with climacteric syndromes were treated with daily oral administration of 6 g RG for 30 days, CMI and STAI A-state scores decreased within normal range. Although the decreased DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the C/D ratio decreased significantly after treatment with RG. CONCLUSIONS: Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly fatigue, insomnia and depression, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in C/D ratio.

Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10.

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Pharmacopsychiatry 1997 Sep;30 Suppl 2:81-5

The special extract of St. John's wort, LI 160, exhibited a superior antidepressant efficacy compared to placebo in several controlled trials. Two further trials demonstrated a similar reduction of depressive symptomatology under LI 160 compared to tricyclics. All these trials were performed in mildly to moderately depressed patients. The present investigation was a randomized, controlled, multicentre, 6-week trial comparing 1800 mg LI 160/die to 150 mg imipramine/die in severely depressed patients according to ICD-10. The main efficacy parameter, a reduction of the total score of the Hamilton Depression Scale, proved both treatment regimens very effective at the end of the 6 week treatment period (mean values 25.3 to 14.5 in the LI 160 group and 26.1 to 13.6 in the imipramine group), but not statistically equivalent within a a-priori defined 25% interval of deviation. The analysis of subgroups with more than a 33% and 50% reduction of the HAMD total score justified the assumption of equivalence

within a 25% deviation interval. This view was also supported by the global efficacy ratings from patients and investigators. Regarding adverse events, the nonrejection of the nonequivalence hypothesis denotes a superiority of the herbal antidepressant. These main result indicate that LI 160 might be a treatment alternative to the synthetic tricyclic antidepressant imipramine in the majority of severe forms of depressions. However, more studies of this type must be performed before a stronger recommendation can be made.

Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group.

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Int J Clin Pharmacol Res 1999;19(3):89-99

A randomized, multicenter, double-blind, parallel group study was performed to assess the effects of a standardized ginseng extract compared with those of a placebo on quality of life (QoL) and on physiological parameters in symptomatic postmenopausal women. Validated questionnaires [Psychological General Well-Being (PGWB) index, Women's Health Questionnaire (WHQ)] and Visual Analogue (VA) scales were used to assess the effects of the extract on QoL at baseline and after 16 weeks' treatment with either the ginseng extract or placebo. To assess the efficacy of ginseng on postmenopausal symptoms, physiological parameters [follicle-stimulating hormone (FSH) and estradiol levels, endometrial thickness, maturity index and vaginal pH] were recorded at the same time points. Of the 384 randomized patients (mean age 53.5 +/- 4.0 years), the questionnaires were completed by 193 women treated with ginseng and 191 treated with placebo. With regard to the primary endpoint (total score of the PGWB index) the extract showed only a tendency for a slightly better overall symptomatic relief (p < 0.1). Exploratory analysis of PGWB subsets, however, reported p-values < 0.05 for depression, well-being and health subscales in favor of ginseng compared with placebo. No statistically significant effects were seen for the WHQ and the VA scales or the physiological parameters, including vasomotor symptoms (hot flushes). The positive effects of ginseng on health-related QoL in menopausal women should be further investigated. This study shows, however, that the beneficial effects of ginseng are most likely not mediated by hormone replacement-like effects, as physiological parameters such as FSH and estradiol levels, endometrial thickness, maturity index and vaginal pH were not affected by the treatment.

Comparison of St John's wort and imipramine for treating depression: randomised controlled trial.

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BMJ 2000 Sep 2;321(7260):536-9

OBJECTIVES: To compare the efficacy and tolerability of Hypericum perforatum (St John's wort extract) with imipramine in patients with mild to moderate depression. DESIGN: Randomised, multicentre, double blind, parallel group trial. SETTING: 40 outpatient clinics in Germany. Participants: 324 outpatients with mild to moderate depression. INTERVENTION: 75 mg imipramine twice daily or 250 mg hypericum extract ZE 117 twice daily for 6 weeks. MAIN OUTCOME MEASURES: Hamilton depression rating scale, clinical global impression scale, and patient's global impression scale. RESULTS: Among the 157 participants taking hypericum mean scores on the Hamilton depression scale decreased from 22.4 at baseline to 12.00 at end point; among the 167 participants taking imipramine they fell from 22.1 to 12.75. Mean clinical global impression scores at end point were 2.22 out of 7 for the hypericum group and 2.42 for the imipramine group. On the 7 point self assessments of global improvement completed by participants (score of 1 indicating "very much improved" and 7 indicating "very much deteriorated") mean scores were 2.44 in the hypericum group and 2.60 in the imipramine group. None of the differences between treatment groups were significant. However, the mean score on the anxiety-somatisation subscale of the Hamilton scale (3.79 in the hypericum group and 4.26 in the imipramine group) indicated a significant advantage for hypericum relative to imipramine. Mean scores on the 5 point scale used by participants to assess tolerability (score of 1 indicating excellent tolerability and 5 indicating very poor tolerability) were better for hypericum (1.67) than imipramine (2.35). Adverse events occurred in 62/157 (39%) participants taking hypericum and in 105/167 (63%) taking imipramine. 4 (3%) participants taking hypericum withdrew because of adverse events compared with 26 (16%) taking imipramine. CONCLUSIONS: This Hypericum perforatum extract is therapeutically equivalent to imipramine in treating mild to moderate depression, but patients tolerate hypericum better.

Dehydroepiandrosterone (DHEA) treatment of depression.

Wolkowitz OM; Reus VI; Roberts E; Manfredi F; Chan T; Raum WJ; Ormiston S ; Johnson R; Canick J; Brizendine L; Weingartner H Department of Psychiatry, University of California, San Francisco, School of Medicine 94143-0984, USA.

Biol Psychiatry (United States) Feb 1 1997, 41 (3) p311-8

Dehydroepiandrosterone (DHEA) and its sulfate, DHEA-S, are plentiful adrenal steroid hormones that decrease with aging and may have significant neuropsychiatric effects. In this study, six middle-aged and elderly patients with major depression and low basal plasma DHEA f1p4or DHEA-S levels were openly administered DHEA (30-90 mg/d x 4 weeks) in doses sufficient to achieve circulating plasma levels observed in younger healthy individuals. Depression ratings, as well as aspects of memory performance significantly improved. One treatment-resistant patient received extended treatment with DHEA for 6 months: her depression ratings improved 48-72% and her semantic memory performance improved 63%. These measures returned to baseline after treatment ended. In

both studies, improvements in depression ratings and memory performance were directly related to increases in plasma levels of DHEA and DHEA-S and to increases in their ratios with plasma cortisol levels. These preliminary data suggest DHEA may have antidepressant and promemory effects and should encourage double-blind trials in depressed patients.

Double-blind treatment of major depression with dehydroepiandrosterone.

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Am J Psychiatry 1999 Apr;156(4):646-9

OBJECTIVE: This study was designed to assess possible antidepressant effects of dehydroepiandrosterone (DHEA), an abundant adrenocortical hormone in humans.

METHOD: Twenty-two patients with major depression, either medication-free or on stabilized antidepressant regimens, received either DHEA (maximum dose = 90 mg/day) or placebo for 6 weeks in a double-blind manner and were rated at baseline and at the end of the 6 weeks with the Hamilton Depression Rating Scale. Patients previously stabilized with antidepressants had the study medication added to that regimen; others received DHEA or placebo alone.

RESULTS: DHEA was associated with a significantly greater decrease in Hamilton depression scale ratings than was placebo. Five of the 11 patients treated with DHEA, compared with none of the 11 given placebo, showed a 50% decrease or greater in depressive symptoms.

CONCLUSIONS: These results suggest that DHEA treatment may have significant antidepressant effects in some patients with major depression. Further, larger-scale trials are warranted.

Replacement of DHEA in aging men and women. Potential remedial effects.

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Ann N Y Acad Sci (UNITED STATES) Dec 29 1995, 774 p128-42

DHEA in appropriate replacement doses appears to have remedial effects with respect to its ability to induce an anabolic growth factor, increase muscle strength and lean body mass, activate immune function, and enhance quality of life in aging men and women, with no significant adverse effects. Further studies are needed to confirm and extend our current results, particularly the gender differences.

The use of diet and dietary components in the study of factors controlling affect in humans: a review.

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J Psychiatry Neurosci 1993 Nov;18(5):235-44

Although one of the first biological treatments of a major psychiatric disorder was the dietary treatment of pellagra, the use of diet and dietary components in the study of psychopathology has not aroused much interest. This article reviews three areas in which the dietary approach has provided interesting information. The tryptophan depletion strategy uses a mixture of amino acids devoid of tryptophan to lower brain tryptophan in order to study the symptoms that can be elicited. One effect of tryptophan depletion is a lowering of mood, the magnitude of which seems to depend on the baseline state of the subject. Therefore, recovered depressed patients often undergo an acute relapse, while normal subjects show more moderate changes of mood. Totally euthymic subjects show no lowering of mood, but subjects with high normal depression scale scores or subjects with a family history of depression show a moderate lowering of mood. These data indicate that low serotonin levels alone cannot cause depression. However, serotonin does have a direct effect on mood, and low levels of serotonin contribute to the etiology of depression in some depressed patients. Folic acid deficiency causes a lowering of brain serotonin in rats, and of cerebrospinal fluid 5-hydroxyindoleacetic acid in humans. There is a high incidence of folate deficiency in depression, and there are indications in the literature that some depressed patients who are folate deficient respond to folate administration. Folate deficiency is known to lower levels of S-adenosylmethionine, and S-adenosylmethionine is an antidepressant that raises brain serotonin levels. These data suggest that low levels of serotonin in some depressed patients may be a secondary consequence of low levels of S-adenosylmethionine. They also suggest that the dietary intake and psychopharmacological action of methionine, the precursor of S-adenosylmethionine, should be studied in patients with depression. Normal meals have definite effects on mood and performance in humans. The composition of the meal, in terms of protein and carbohydrate content, can influence these behaviors. Because protein and carbohydrate meals can influence brain serotonin in rats, these effects in humans have usually been interpreted in terms of altered serotonin functioning. However, the current balance of evidence is against the involvement of serotonin in the acute effects of protein and carbohydrate meals in humans. The underlying mechanisms involved are unknown, but there are a variety of possibilities.(ABSTRACT TRUNCATED AT 400 WORDS)

Folic acid and psychopathology.

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Prog Neuropsychopharmacol Biol Psychiatry 1989;13(6):841-63

1. The incidence of folic acid deficiency is high in patients with various psychiatric isorders including depression, dementia and schizophrenia. 2. In epileptics on anticonvulsants, folate deficiency often occurs because anticonvulsants inhibit folate absorption. In these patients folate deficiency is often associated with psychiatric symptoms. 3. In medical patients psychiatric symptoms occur more frequently, and in psychiatric patients symptoms are more severe, in those with folate deficiency than in those with normal levels. 4. Many open studies have demonstrated therapeutic effects of folate administration on psychiatric symptoms in folate deficient patients. 5. Several placebo-controlled studies have not demonstrated therapeutic effects, possibly because the doses they used (15-20 mg/day) are known to be toxic and to cause mental symptoms. 6. Two placebo-controlled studies have demonstrated beneficial effects of folic acid administration, one in patients with a syndrome of psychiatric and neuropsychological changes associated with folate deficiency and the other in patients on long-term lithium therapy. In the latter study the dose was only 0.2 mg/day. 7. Folic acid deficiency is known to lower brain S-adenosylmethionine and 5-hydroxytryptamine. S-Adenosylmethionine, which has antidepressant properties, raises brain 5-hydroxytryptamine. Thus, depression associated with folate deficiency is probably related to low brain 5HT. 8. S-Adenosylmethionine is involved in many methylation reactions, including methylation of membrane phospholipids, which influences membrane properties. This may explain the wide variety of symptoms associated with folate deficiency. 9. Because the costs and risks associated with low doses of folic acid (up to 0.5 mg/day) are small, folic acid should be given as an adjunct in the treatment of patients with unipolar or bipolar affective disorders and anorexia, epileptics on anticonvulsants, geriatric patients with mental symptoms and patients with gastrointestinal disorders who exhibit psychiatric symptoms. 10. Although the majority of the patients listed above will probably not be helped by folic acid therapy, a significant minority are likely to have folate-responsive symptoms.

Relationship between dopamine-stimulated phospholipid methylation and the single-carbon folate pathway.

Zhao R, Chen Y, Tan W, Waly M, Sharma A, Stover P, Rosowsky A, Malewicz B, Deth RC. Department of Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts 02115, USA.

J Neurochem 2001 Aug;78(4):788-96

In a previous study we demonstrated the ability of dopamine (DA) to stimulate phospholipid methylation (PLM) via a novel mechanism involving the D4 dopamine receptor (D4R) in which single-carbon folates appeared to be the primary source of methyl groups. To further understand the relationship between D4R-mediated PLM and folate metabolism, we examined the effect of several folate pathway interventions on the level of basal and DA-stimulated incorporation of [14C]-labeled formate into phospholipids in cultured SH-SY5Y neuroblastoma cells. These interventions included: (i) Overexpression of methenyltetrahydrofolate synthetase (MTHFS). (ii) Treatment with 5-formylTHF. (iii) Treatment with the MTHFS inhibitor 5-formyltetrahydrohomofolic acid (5-

formylTHHF). (iv) Growth in nucleoside-free media. 31P-NMR was also used to follow DA-induced changes in cell phospholipid composition. MTHFS overexpression and 5-formylTHHF treatment, both of which lower 5-methylTHF levels, each reduced basal PLM and its stimulation by DA. In contrast, 5-formylTHF, which increases 5-methylTHF, caused a dose-dependent increase in both basal and DA-stimulated PLM. Growth in nucleoside-free media caused time-dependent changes in PLM, which were due to the absence of purine nucleosides. While basal PLM was maintained at a reduced level, DA-stimulated PLM was initially increased followed by a later decrease. Together, these findings indicate a close functional relationship between single-carbon folate metabolism and DA-stimulated PLM, consistent with a role for 5-methylTHF as the methyl donor for the D4R-mediated process.

Antidepressive effectiveness of a highly dosed hypericum extract

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Munchener Medizinische Wochenschrift (Germany), 1996, 138/3 (35-39)

Study objective: Clinical effectiveness of the hypericum extract LI 160 in cases of mild and moderate depression.

Design: Randomized, double-blind placebo-controlled study with subsequent active medication in both patient groups. Patients: 102 outpatients with major depression in mild or moderate form according to DSM-IIIR. Intervention: Daily dosage 3 x 1 coated tablet LI 160 (equivalent to 900 mg hypericum extract) or placebo for four weeks with subsequent two weeks active medication in both medication groups. Endpoint: Changes of depressive symptoms according to psychometric tests.

Main results: The total Hamilton score in the active treatment group fell significantly ($p < 0.001$) further (from 21.0 to 8.9) after four weeks than in the placebo group (from 20.4 to 14.4). Significant differences were also shown for v. Zerssen's depressivity scale (D-S) and when evaluating the level of symptoms ($p < 0.01$). The four-week placebo phase was followed by a two week active medication phase in both groups. This also led to a reduction in symptoms in the placebo group that correlated with the changes observed in the verum group during the first two weeks of treatment. Side ffects, in the form of slight sleep disturbances, were only reported by one patient in the verum group.

Conclusion: On account of its antidepressive effectiveness and very good tolerability, the hypericum extract LI 160 can be recommended for treating patients with mild to moderate depression.

St. John's Wort in the treatment of depression

Ernst E.
Fortschritte der Medizin (Germany), 1995, 113/25 (32-33)

St. John's Wort (Hypericum perforatum) has been used to treat a variety of complaints since ancient times. Recent studies have shown that it is clinically effective for the treatment of the symptoms of depression. It has proved superior to placebo, equally as effective as standard medication and has a clear advantage over the latter in terms of side-effects. It follows that, on the basis of our present knowledge, St. John's Wort can be recommended for use as an anti-depressant.

Hypericum perforatum

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Fitoterapia (Italy), 1995, 66/1 (43-68)

H. perforatum is a medicinal plant which has been known in traditional medicine as antiinflammatory and healing agent. Nowadays purified extracts of its aerial parts are used for their antidepressant activity. Furthermore the antiviral activity of hypericin is currently under investigation. This review deals with the botany, chemistry, pharmacology and the clinical efficacy of H. perforatum extracts and of their active constituents, namely hypericin and pseudohypericin.

Psychomotoric performance improvement: Antidepressant therapy with St John's wort

Schmidt U.; Maisenbacher J.; Harrer G.; Kuhn U.
Therapiewoche (Germany), 1995, 45/2 (106+108+110+112)

The following study investigated the influence of a herbal antidepressant containing Hypericum extract, on the cognitive performance in patients with anxiety depression. In the course of the 4-week treatment, the patients showed a reduction in both the state of anxiety and depression. The responder rate determined with the Hamilton Depression Scale was nearly 70%. Tolerance was very good. There weren't observed any adverse drug effects. The psychometric tests well established in traffic medicine could show, in comparison with the untreated control group, that the antidepressant therapy did not impair concentration nor reactivity. The data from the responder group indicates that the antidepressant therapy even caused an increase in complex cognitive performances which exceed the known training effect of these tests.

Hypericum in the treatment of seasonal affective disorders

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S29-S33)

Seasonal affective disorder (SAD) represents a subgroup of major depression with a regular occurrence of symptoms in autumn/winter and full remission in spring/summer. Light therapy (LT) has become the standard treatment of this type of depression. Apart from this, pharmacotherapy with antidepressants also seems to provide an improvement of SAD symptoms. The aim of this controlled, single-blind study was to evaluate if hypericum, a plant extract, could be beneficial in treating SAD patients and whether the combination with LT would be additionally advantageous. Patients who fulfilled DSM-III-R criteria for major depression with seasonal pattern were randomized in a 4-week treatment study with 900 mg of hypericum per day combined with either bright (3000 lux, n = 10) or dim (< 300 lux, n = 10) light condition. Light therapy was applied for 2 hours daily. We found a significant (MANOVA, P < .001) reduction of the Hamilton Depression Scale score in both groups but no significant difference between the two groups. Our data suggest that pharmacologic treatment with hypericum may be an efficient therapy in patients with seasonal affective disorder.

Effectiveness and tolerance of the hypericum extract LI 160 compared to maprotiline: A multicenter double-blind study

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S24-S28)

A randomized, double-blind study examining the effectiveness and tolerance of a standardized hypericum preparation when compared to maprotiline was performed in a group of 102 patients with depression, in accordance with ICD-10, F 32.1. The study was conducted in the offices of neurology and psychiatry specialists. The patients received, over a period of 4 weeks, either 3 x 300 mg of the hypericum extract or 3 x 25 mg maprotiline pills of identical appearance. Effectiveness was determined using the Hamilton Depression Scale (HAMD), the Depression Scale according to von Zerssen (D-S), and the Clinical Global Impression Scale (CGI). The total score of the HAMD scale dropped during the 4 weeks of therapy in both treatment groups by about 50%. The mean values of the D-S scale and the CGI scale showed similar results, and after 4 weeks of therapy, no significant differences in either treatment group were noticed. The onset of the effects occurred up to the second week of treatment, but were observed earlier with maprotiline than with the hypericum extract. On the other hand, maprotiline treatment resulted in more cases of tiredness, mouth dryness, and heart complaints.

Effectiveness and tolerance of the hypericum extract LI 160 in comparison with imipramine: Randomized double-blind study with 135 outpatients

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S19-S23)

In a double-blind comparative study, 135 depressed patients were treated in 20 centers. Inclusion diagnoses were typical depressions with single episode (296.2), several episodes (296.3), depressive neurosis (300.4), and adjustment disorder with depressed mood (309.0) in accordance with DSM-III-R. The dosage was 3 x 300 mg hypericum extract LI 160 or 3 x 25 mg imipramine daily. The treatment lasted for 6 weeks. Main assessment criteria were the Hamilton Depression Scale (HAMD), the Depression Scale according to von Zerssen (D-S) and the Clinical Global Impressions (CGI). In both treatment groups, a parallel reduction of the Hamilton score from 20.2 to 8.8 (LI 160, n = 67) or from 19.4 to 10.7 (imipramine, n = 68), and the transformed D-S point values from 39.6 to 27.2 (LI 160) and 39.0 to 29.2 (imipramine) were found. The analysis of CGI revealed comparable results in both treatment groups. Clinically relevant changes of the safety parameters were not found. In the LI 160 group fewer and milder side effects were found as compared to imipramine.

Multicenter double-blind study examining the antidepressant effectiveness of the hypericum extract LI 160

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S15-S18)

Seventy-two depressive patients of 11 physicians' practices were treated in a double-blind study for a period of 6 weeks either with hypericum extract LI 160 or with placebo. Inclusion criterion was a major depression in accordance with DSM-III-R. The changes were assessed using four psychometric scales (HAMD, D-S, BEB, CGI). After 4 weeks of therapy, the statistical evaluation revealed a significant improvement in all four psychometric tests in the active group as compared to the placebo group. After switching the placebo group to active treatment (5th to 6th week of therapy), significant improvements were found in the original placebo group. No serious side effects were observed.

Hypericum treatment of mild depressions with somatic symptoms

Hubner WD; Lande S; Podzuweit H
Lichtwer Pharma GmbH, Berlin, Germany.
J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S12-S14)

In a randomized, placebo-controlled, double-blind study, 39 patients with depression with somatic symptoms were treated with hypericum extract LI 160. The therapy lasted for 4 weeks; the dosage was 300 mg three times daily. At the onset of the study as well as after 2 and 4 weeks, the following criteria were analyzed: HAMD, B-L, CGI, and vegetative symptoms. The results show a significant improvement in the active treatment group at the 5% level as compared to placebo. Seventy percent of the patients treated with LI 160 were free of symptoms after 4 weeks. Typical symptoms of the depression such as lack of activity, tiredness, fatigue, and disturbed sleep, were especially responsive. In no case were any undesirable side effects observed.

St. Johns' wort: A prescription from nature against depressions

Sattler S.; Schutt H.
Therapiewoche (Germany), 1994, 44/14 (808+811-815)

The various use of St. Johns' wort, especially for depressive disorders, is based on the specific pattern of ingredients. Characteristic constituents for this plant are hypericins, hyperforine and flavonoids. These flavonoids are inhibitors of type A monoamino-oxidase in vitro. An improved utilisation of light is due to hypericin. In agreement of common experiences clinical studies prove the effectiveness of Hypericum perforatum on minor and moderate depressive disorders comparable to tricyclic antidepressants used in therapy. Therefore Hypericum perforatum represents a high potent drug for phytotherapy including good compatibility and low risk of side effects.

Extract of St. John's wort in the treatment of depression - Attention and reaction remain unimpaired

Schmidt U.; Sommer H.
Fortschr. Med. (Germany), 1993, 111/19 (37-40)

Method: In a placebo-controlled, randomized, double-blind trial involving outpatients with mild to moderately severe depression, an extract of St. John's wort (Hypericum), LI 160, a herbal antidepressant was tested for efficacy and tolerability, as well as for possible negative effects on cognitive performance.

Results: The responder rate to treatment with the extract was 66,6% as compared with only 26,7% with placebo. The treatment was very well tolerated; only in two patients did transient minor side effects occur under LI 160. No impairment of cognitive performance was observed: during the trial, Hypericum did not lead to any impairment of attention, concentration or reaction.

Investigations of the antidepressive effects of St. Johns Wort

Sparenberg B.; Demisch L.; Holzl J.
Pz Wiss. (Germany), 1993, 138/2 (50-54)

Extracts from Hypericum perforatum are used in the treatment of symptoms related to depressive disorders, although the active principle is not yet elucidated. Recent investigations showed a significant inhibition of MAO type-A in vitro by extracts from Hypericum. Therefore a number of Hypericum components have been tested for their MAO-inhibitory potency in vitro. The results revealed flavonoidaglyca as the active substances. The glycosides are less active, only quercitrin shows inhibition of MAO. Furthermore 1,3,6,7-tetrahydroxyxanthone was found to be a strong inhibitor of MAO A in vitro.

Experimental animal studies of the psychotropic activity of a Hypericum extract

Okpanyi S.N.; Weischer M.L.
Arzneim.-Forsch./Drug Res. (Germany, West), 1987, 37/1 (10-13)

Extracts of Hypericum perforatum (Psychotonin(Reg.trademark) M) (St. John's wort) with known concentrations of hypericin were tested in several models generally accepted as screening methods in experimental animal studies for the recognition of psychotropic, and in particular of antidepressant activity. Hypericum extract enhanced the exploratory activity of mice in a foreign environment, significantly prolonged the narcotic sleeping time dose-dependently, and within a narrow dose range exhibited reserpine antagonism. Similar to most other antidepressants, hypericum extract enhanced significantly the activity of mice in the water wheel test and after a prolonged daily administration decreased aggressiveness in socially isolated male mice. The presented data in addition to the already proven clinical efficacy justify the use of standardised Hypericum extract in the treatment of mild to moderate depression.

Plasma tryptophan and five other amino acids in depressed and normal subjects.

DeMyer, Marian K.; Shea, Philip A.; Hendrie, Hugh C.; Yoshimura,
Archives of General Psychiatry 38(6):642-646, 1981

The ratio of plasma tryptophan (TRP) to five other neutral amino acids (TRP/5aa ratio) was examined in depressed Ss and normal controls. Plasma TRP (free and total), phenylalanine (PHE), tyrosine (TYR), leucine, isoleucine, and valine were measured on three days. When depression was most severe, depressed patients

had lower TRP/5aa ratios and total TRP levels and higher PHE and TYR levels. As Hamilton depression scores improved, the plasma TRP/5aa ratios increased significantly. The finding tends to support the idea that changes in brain serotonin level reflect changes in depression severity. 41 references.

Trace amine deficit in depressive illness: the phenylalanine connexion.

Sandler, M.; Ruthven, C. R. J.; Goodwin, B. L.; Reynolds, G. P.; Rao, V. A. R.; Coppen, A.
Acta Psychiatrica Scandinavica 61(Suppl. 280):29-39, 1980

Preliminary studies of deficiencies of three trace amines (phenylethylamine, tyramine, and octopamine) in patients with depressive illness are described. Data from two groups of depressed Ss and control Ss indicate that the mean output of p-hydroxyphenylacetic acid and p-hydroxymandelic acid in urine is significantly lower in depressed patients than in control Ss. Both the patients as a whole and the male patients as a subset possessed significantly lower cerebrospinal fluid phenylacetic acid concentrations than did control Ss. Three patients characterized by severe endogenous depression features and who responded poorly to tricyclic drugs had very low excretion values of p-hydroxymandelic acid and p-hydroxyphenylacetic acid, although the other metabolites were normal. A panel discussion of these findings is appended. 40 references.

Phenylalanine levels in endogenous psychoses.

Uebelhack, Ralf; Franke, Leonora; Kitzrow, Werner; Seidel, Karl.
Psychiatrie, Neurologie und Medizinische Psychologie 32(10):631-633, 1980

The effects of phenylalanine levels on 65 depressive and psychotic patients were made over a period of 14 days. Patients were kept on a protein free diet for 24 hours prior to the test. Patients received doses of L-phenylalanine at a rate of 100mg/kg. Blood samples drawn hourly were analyzed for amino acid content. Phenylalanine doses were found to be effective for 48 hours. EEG examinations were given to 29 patients both before and after the test. Four female patients experienced hallucinations during the first 4 hours. No conclusions were reached regarding the relation of deviant phenylalanine levels to psychoses. Six patients experienced a remission of psychotic symptoms beginning 2 to 3 weeks after the experiment. A decrease in psychotic symptomatology was seen in 16 depressive patients. 11 references.

Evaluation of the relative potency of individual competing amino acids to tryptophan transport in endogenously depressed patients.

Moller, Svend E.
Psychiatry Research 3(2):141-150, 1980

The relative potency of the individual amino acids as competitive inhibitors of tryptophan transport into the human brain was evaluated retrospectively; the combination of competitors that yields the highest predictive value of the plasma tryptophan ratio for the course of treatment of depressed patients with L-tryptophan was also examined. Phenylalanine consistently reduced, and isoleucine slightly reduced the predictive value of the plasma tryptophan ratio. The ratio of tryptophan to the sum of valine, leucine, and tyrosine was identified as most predictive for the therapeutic response to tryptophan. L-tryptophan responders showed a normal plasma total tryptophan concentration as did the nonresponders, whereas the concentration of the three competitors was significantly elevated. It is concluded that while the plasma ratio of tryptophan to the sum of valine, leucine, and tyrosine is a useful predictor of the course of depressives on L-tryptophan, it does not definitely separate out the L-tryptophan responders from the control subjects.

Amino acids in mental illness.

Yaryura-Tobias, J. A.
Biological psychiatry today. Vol. B Amsterdam, Elsevier/North Holland, 1979, p1581-4

Research on the influence of several aromatic amino acids in psychiatric disturbances is reviewed, with emphasis on phenylalanine, tyrosine, and tryptophan. The principles of a dopaminergic theory of schizophrenia and of levodopa therapy in neuropsychiatric disorders are treated, along with the role of phenylalanine in phenylketonuria, depression, and schizophrenia. The relation of tryptophan to Hartnup disease, schizophrenia, depression, manic-depression, manic-depressive illness, insomnia, and obsessive-compulsive disorders is also treated. It is concluded that these compounds have important roles in brain physiology and may be involved in the physiopathology of certain mental disorders and/or their treatment.

Depression, pregnancy and phenylalanine.

Portnoy, Mario Ernesto.
Neuropisiquiatria (Buenos Aires) 8(1):60-64, 1977

A case study of a mentally depressed pregnant woman who was successfully treated with phenylalanine is reported. The subject was a 34-year-old Argentine woman, married for 5 years and childless. Once the subject was administered phenylalanine, her condition improved. It is noted that a heightened dosage of the drug is required during pregnancy, and that this has no complicating effect on the mother or the child. To check this, the subject's baby was observed for a year after

birth. The physiological action of the drug is analyzed, and the progress of the treatment through pregnancy is charted. 17 references.

Phenylethylamine and glucose in true depression.

Journal of Orthomolecular Psychiatry (Regina) 5(3):199-202, 1976

The relationship between urinary phenylethylamine (PEA) and oral glucose tolerance tests in true depression was investigated in 12 depressives who were resistant to psychotherapy, chemotherapy, and electroconvulsive shock therapy. All medication was discontinued 72 hours prior to testing. Urinary PEA was measured 24 hours before and 72 hours after patients were placed on a 350g carbohydrate load diet. Clinical psychiatric examinations were also performed before, during, and after this treatment. Results revealed severely depressed PEA levels in all patients and disturbed glucose metabolism in 10 of the 12. Improvement was shown by the fifth day of the diet, and good remission of symptoms began by the second week. Side effects, which included mild headache, low blood pressure, and agitation,were few. It is concluded that D-phenylalanine and DL-phenylalanine are thus shown to be antidepressants in true depressives whose illness is caused by biochemical deficiencies, and that the presence of a glucose imbalance in the patients studied may suggest a monoamine disorder as the cause of depression. 28 references.

Therapeutic action of D-phenylalanine in Parkinson's disease.

Heller B, Fischer E, Martin R
Arzneimittelforschung 1976 Apr;26(4):577-9

An open field trial of D-phenylalanine was made in 15 patients with Parkinson's disease of 6 months' to 13 years' duration. All medication was suspended 10 days before the trial, and the patients received only 200mg-500mg D-phenylalanine daily, divided into 2 doses, for 4 weeks. Positive results were highly significant in relation to rigidity, walking disabilities, speech difficulties, and mental depression, but no significant therapeutic results were obtained in regard to tremor. The therapeutic action on the total development of the disease may be considered highly significant. The results suggest a special cholinergic origin of tremor in Parkinson's disease, and in these cases a combination of the amino acid with anticholinergic agents should be tried.

Effects of D-phenylalanine on clinical picture and phenethylaminuria in depression.

Biological Psychiatry 10(2):235-239, 1975

The administration of D-phenylalanine in 11 cases of depression with low urinary phenethylamine output was studied. It was found that the administration of D-phenylalanine to depressed patients in daily oral doses of 100-200mg produced an improvement of the clinical state associated with an increase in the daily urinary phenethylamine output.

Phenylalanine Effective Against Depression

Treatment of endogenous depression with d,1-phenylalanine and d-phenylalanine is reported. Ss all had long-term endogenous depression, and all had been treated unsucessfully with imipramine like drugs and/or inhibitors of monoamineoxidase. Ss were given daily oral doses of 50mg or 100mg of either drug over a period of 15 days. Complete euthymia was obtained in 74% of the Ss between 1 and 13 days of treatment. Side-effects were minimal and in no case required termination of treatment. 13 references. (Author abstract modified)

Phenylalanine for endogenous depression.

Yaryura Tobias J.A.; Heller B.; Spatz H.; Fischer E.
North Nassau Ment. Hlth Cent., Manhasset, Long Island, N.Y. 11030 United States
Journal of Orthomolecular Psychiatry 1974, 3/2 (80-81)

Phenylalanine was administered to patients suffering from endogenous depression. Although the experimental trial was short and the dosage small, it seems that some forms of endogenous depression responded well to phenylalanine therapy, mainly with the dextrorotatory form.

Rapidity of onset of the antidepressant effect of parenteral S-adenosyl-L-methionine

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Depression Research Program, Massachusetts General Hospital, Boston 02114, USA.
Psychiatry Res 1995 Apr 28;56(3):295-7

A possible method of reducing the delay in antidepressant response is to use S-adenosyl-L-methionine (SAMe), a naturally occurring compound that appears to have a rapid onset of effect in the treatment of depression. In this open, multicenter study, 195 patients were given 400 mg of SAMe, and no serious adverse events were reported. Further studies with a double-blind design are needed to confirm this preliminary indication that SAMe is a relatively safe and fast-acting antidepressant.

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.

Primary fibromyalgia is responsive to S-adenosyl-L-methionine

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/7 (797-806)

Forty-seven patients with primary fibromyalgia were treated with S-adenosyl-L-methionine (SAMe) 200 mg intramuscularly once daily, plus SAMe 400 mg orally twice daily, for 6 weeks. The treatment was preceded by a 7-day drug-free run-in washout period. SAMe significantly decreased tenderness of painful sites, significantly improved general well-being, and significantly reduced the mean scores (baseline vs day 42) for the Hamilton Rating Scale for Depression, the Zung SelRating Scale, the Hamilton Rating Scale for Anxiety, and Lorish and Maisiak's Face Scale. SAMe was well tolerated in all patients and no adverse side effects were reported.

S-adenosyl-L-methionine in Sjogren's syndrome and fibromyalgia

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Division of Rheumatology, Institute of Internal Medicine, University of Padova,Padova Italy
Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/6 (699-706)

The subjects were 30 patients aged 25 to 60 years (mean, 51 years) with primary Sjogren's syndrome, both Sjogren's syndrome and primary fibromyalgia, or fibromyalgia only. Each patient received 200 mg of S-adenosyl-L-methionine (SAMe) by intramuscular injection daily. After 4 weeks of treatment, in the 10 patients with Sjogren's syndrome, disease symptoms and scores on Zung's SelRating Scale for Depression showed a nonsignificant decrease; a reduction in mean scores on Hamilton's Rating Scale for Depression, however, was statistically significant ($P < 0.05$). In the 10 patients with both Sjogren's syndrome and fibromyalgia, no significant changes in symptoms, depression scale scores, or scores on a pain-severity scale were found; however, the numbers of tender points and painful areas were reduced significantly ($P < 0.01$). In the 10 patients with fibromyalgia, symptoms of fibromyalgia, numbers of tender points and painful areas, pain severity scores, and scores on both depression scales were reduced significantly ($P < 0.01$). No adverse side effects were reported. The results indicate that SAMe can reduce the symptoms of fibromyalgia and improve mood; further studies are warranted.

Effects of S-adenosyl-L-methionine on cognitive and vigilance functions in the elderly

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Teaching Department of Neurology, General Hospital,Venice Italy
Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/6 (682-689)

Forty elderly patients with impaired cognition and vigilance functions associated with primary or secondary organic brain syndrome were treated with S-adenosyl-L-methionine (SAMe) for 2 months. Patients scoring 17 or higher on Hamilton's Rating Scale for Depression (HRSD) were excluded from the study. The SAMe dosing schedule was 400 mg intravenously during the first 20 days, and 200 mg intramuscularly plus 400 mg orally twice daily for another 40 days. Examinations were performed using the Mini-Mental State Examination (MMSE) and the Sandoz Clinical Assessment Geriatric Scale (SCAG) at time 0 (baseline) and on days 20 and 60 of treatment. Statistically significant differences ($P < 0.01$) were observed in MMSE and SCAG total scores on day 60 versus baseline. Significant improvements were observed in 4 out of 19 items on the SCAG versus baseline on day 20, and in 13 out of 19 items versus baseline on day 60. No adverse side effects were reported.

Results of treatment with s-adenosyl-l-methionine in patients with major depression and internal illnesses

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/6 (666-674)

Forty-eight patients with major depression associated with internal illnesses of various origins were enrolled for 4 weeks of treatment with S-adenosyl-L-methionine (SAMe). The medication was administered parenterally (400 mg daily either intravenously or intramuscularly) in inpatients and orally (800 mg daily) in outpatients. Evaluations were performed via Beck's Depression Inventory (BDI) by comparing the scores on day 28 with baseline values. Statistically significant differences were observed ($P < 0.01$). Although minor adverse side effects were reported, they were not severe enough to withdraw medication. SAMe treatment proved to be effective and relatively safe in depressed patients with associated internal illnesses.

S-adenosyl-l-methionine (SAMe) as antidepressant: Meta-analysis of clinical studies

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Acta Neurol Scand Suppl 1994;154:7-14

Introduction - S-adenosyl-l-methionine (SAMe) is a naturally-occurring substance which is a major source of methyl groups in the brain. Material and methods - We conducted a meta-analysis of the studies on SAMe to assess the efficacy of this compound in the treatment of depression compared with placebo and standard tricyclic antidepressants. Results - Our meta-analysis showed a greater response rate with SAMe when compared with placebo, with a global effect size ranging from 27% to 38% depending on the definition of response, and an antidepressant effect comparable with that of standard tricyclic antidepressants. Conclusion - The efficacy of SAMe in treating depressive syndromes and disorders is superior with that of placebo and comparable to that of standard tricyclic antidepressants. Since SAMe is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression.

S-adenosyl-L-methionine in the treatment of major depression complicating chronic alcoholism

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/1 (83-92)

S-adenosyl-L-methionine (SAMe) is a methyl donor endowed with both antidepressant and detoxifying activity. In a 4-week trial, 40 alcoholic patients with major depression received 200 mg of SAMe daily administered intravenously and 400 mg BID administered orally. After a 1-week placebo period during which placebo responders were eliminated, patients were evaluated with the Hamilton Rating Scale for Depression, the Zung Sel Rating Scale for depression, the Hamilton Rating Scale for Anxiety, and the Lorish and Maisiak face scale at baseline and at days 7, 14, 21, and 28. Standard laboratory values were measured at baseline and at the completion of the trial. Significant improvements were seen in most psychometric scores beginning on day 14 and continuing through the end of the study. Baseline values for gamma-glutamyltranspeptidase, alkaline phosphatase, bilirubin, and mean corpuscular volume dropped dramatically and, in some cases, returned to normal. No adverse reactions were reported. Although standard antidepressant therapy has very often been unsuccessful in treating depression in these patients, SAMe proved to be well tolerated at the study dosage and was effective in reducing depression.

Clinical evaluation of S-adenosyl-L-methionine versus transcutaneous electrical nerve stimulation in primary fibromyalgia

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Ospedale Santoro, Rehabilitation Center,Trieste Italy
Current Therapeutic Research - Clinical and Experimental (United States) 1993, 53/2 (222-229)

The effects of S-adenosyl-L-methionine (SAMe) and transcutaneous electrical nerve stimulation (TENS) were evaluated in a 6-week controlled trial of 30 patients with primary fibromyalgia. Unlike TENS, SAMe significantly decreased the total number of tender points, had a significant beneficial effect on the subjective symptoms of pain and fatigue, and significantly reduced the scores on the Hamilton Depression and Anxiety Rating Scales and Zung's SelRating Scale for Depression. At the end of treatment, patients in the TENS group exhibited significantly reduced scores on the Hamilton Anxiety Scale only.

Double blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women

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Psychother Psychosom 1993;59(1):34-40

S-adenosyl-L-methionine (SAMe) is a naturally occurring substance which is a major source of methyl groups in the brain and has been found in previous studies to be an effective antidepressant. The aim of this study was to assess the efficacy of oral SAMe in the treatment of depressed postmenopausal women in a 30-day double-blind placebo-controlled randomized trial. During the course of the study, 80 women, between the ages of 45 and 59, who were diagnosed as having DSM-III-R major depressive disorder or dysthymia between 6 and 36 months following either natural menopause or hysterectomy, underwent 1 week of single-blind placebo washout, followed by 30 days of double-blind treatment with either SAMe 1,600mg/day or placebo. There was a significantly greater improvement in depressive symptoms in the group treated with SAMe compared to the placebo group from day 10 of the study. Side effects were mild and transient.

S-Adenosyl-methionine (SAMe) as antidepressant

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New Trends in Clinical Neuropharmacology (Italy) 1992, 6/1-4 (11-18)

In 1971 S-Adenosylmethionine (SAMe) entered in clinical research. The clinical trial as well as an extensive clinical practice in Europe and more recently in the United States have shown that SAMe, related to depressive syndromes, is effective as tricyclic, but it has some characteristics which distinguish it from other antidepressant drugs. They are: - absence of side effects particularly at liver level; - rapid effect and therefore short period of latency between administration and therapeutic activity.

Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine

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Special Studies Clinic, Mexican Institute of Psychiatry, Tlalpan.
Psychiatry Res 1992 Dec;44(3):257-62

A double-blind clinical trial was carried out to evaluate the efficacy of S-adenosyl-L-methionine (SAMe) in speeding the onset of action of imipramine (IMI). SAMe is a naturally occurring substance that has been shown to possess antidepressant activity with a rapid mode of onset and minimal side effects. Sixty-three outpatients with moderate to severe depression were included in the study. After an initial 1-week placebo period, only 40 patients entered the active treatment phase. During the first 2 weeks of the trial, half of these patients received 200 mg/day of SAMe intramuscularly, while the other half received placebo. Simultaneously, oral IMI was administered to all patients at a fixed dose of 150 mg/day. The onset of clinical response was determined by evaluating patients every second day. By the end of week 2, the parenteral treatment was

suppressed and IMI was adjusted according to individual needs. Depressive symptoms decreased earlier in the patients who were receiving the SAMe-IMI combination than in those who were receiving the placebo-IMI combination.

Oral S-adenosyl-L-methionine in depression

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Current Therapeutic Research - Clinical and Experimental (United States) 1992, 52/3 (478-485)

The antidepressant activity of oral S-adenosyl-L-methionine (SAMe) was evaluated in a randomized, double-blind, imipramine-controlled trial in 30 patients with major depression. The results suggest that oral SAMe is a safe, effective antidepressant with negligible side effects and a rapid onset of action. Only one patient became hypomanic but did not drop out of the study. SAMe may be useful for patients who cannot tolerate other antidepressant agents or for patients with other risk factors. These findings suggest a role for methylation in the pathophysiology of depression.

Neuroendocrine effects of S-adenosyl-(L)-methionine, a novel putative antidepressant

Fava M, Rosenbaum JF, MacLaughlin R, Falk WE, Pollack MH, Cohen LS, Jones L, Pill L
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J Psychiatr Res 1990;24(2):177-84

S-adenosyl-L-methionine (SAMe), a putative antidepressant, is a naturally occurring substance whose mechanism of action is still a matter of speculation. It has been recently postulated that SAMe may increase the dopaminergic tone in depressed patients. Since dopamine inhibits both thyrotropin (TSH) and prolactin secretion, we investigated the effects of treatment with SAMe on the TSH and prolactin response to thyrotropin-releasing-hormone (TRH) stimulation in 7 depressed outpatient women (mean age: 46.1 plus or minus7.2 years) and 10 depressed outpatient men (mean age: 38.0 plus or minus 10.0 years) participating in a six-week open study of oral SAMe in the treatment of major depression. At the end of the study, there was a significant reduction after treatment with SAMe in the response of both prolactin and TSH to TRH stimulation in the group of derpressed men compared to pre-treatment values. On the other hand, in the group of depressed women, the posttreatment prolactin response to TRH did not appear to change when compared to pre-treatment and the TSH response to TRH challenge tended even to augment slightly after treatment with SAMe. Our

results, at least in depressed men, seem to support the hypothesis of a stimulating effect of SAMe on the dopaminergic system.

The antidepressant potential of oral S-adenosyl-l-methionine

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Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston 02114.
Acta Psychiatr Scand 1990 May;81(5):432-6

S-adenosyl-l-methionine (SAMe), a naturally occurring brain metabolite, has previously been found to be effective and tolerated well in parenteral form as a treatment of major depression. To explore the antidepressant potential of oral SAMe, we conducted an open trial in 20 outpatients with major depression, including those with (n = 9) and without (n = 11) prior history of antidepressant nonresponse. The group as a whole significantly improved with oral SAMe: 7 of 11 non-treatment-resistant and 2 of 9 treatment-resistant patients experienced full antidepressant response. Side effects were mild and transient.

S-Adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism

Friedel HA, Goa KL, Benfield P
ADIS Drug Information Services, Auckland, New Zealand.
Drugs 1989 Sep;38(3):389-416

S-Adenosyl-L-methionine (SAMe) is a naturally occurring molecule distributed to virtually all body tissues and fluids. It is of fundamental importance in a number of biochemical reactions involving enzymatic transmethylation, contributing to the synthesis, activation and/or metabolism of such compounds as hormones, neurotransmitters, nucleic acids, proteins, phospholipids and certain drugs. The administration of a stable salt of SAMe, either orally or parenterallly, has been shown to restore normal hepatic function in the presence of various chronic liver diseases (including alcoholic and non-alcoholic cirrhosis, oestrogen-induced and other forms of cholestasis), to prevent or reverse hepatotoxicity due to several drugs and chemicals such as alcohol, paracetamol (acetaminophen), steroids and lead, and to have antidepressant properties. In all of these studies SAMe has been very well tolerated, a finding of great potential benefit given the well-known adverse effects of tricyclic antidepressants with which it has been compared in a few trials. Thus, with its novel mechanisms of action and good tolerability, SAMe is an interesting new therapeutic agent in several diverse disease conditions, but its relative value remains to be determined in appropriate comparisons with other treatment modalities in current use.

Neuropharmacology of S-adenosyl-L-methionine

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Am J Med 1987 Nov 20;83(5A):95-103

The metabolite S-adenosyl-L-methionine (SAMe), when prepared as the stable p-toluene-sulfonate complex of its sulfate salt and given parenterally in high doses, appears to have mood-elevating effects in depressed adults. The material is remarkably well tolerated when given by injection or intravenous infusion for this purpose, even in elderly or demented patients. Assuming that the toluene sulfonate component is inert, SAMe appears to have central neuropharmacologic effects after systemic injection in high doses. Nevertheless, the functional consequences of these remain unclear and, indeed, the ability of exogenous SAMe to reach the brain, and especially neuronal cytoplasm, is limited. SAMe has small effects on monoamine metabolism and, after injection, appears to have effects on the microviscosity of cell membranes that may be related to stimulation of phospholipid synthesis. The recent introduction of an orally administered form of SAMe for use in the treatment of osteoarthritis promises to stimulate further study of SAMe in disease-associated depression, major depressive disorder, and other neuropsychiatric conditions.

Vitamins in psychiatry. Do they have a role?

Petrie WM, Ban TA
Drugs 1985 Jul;30(1):58-65

Deficiencies of specific vitamins produce consistent symptoms of psychiatric disorder. Thiamine deficiency, which is common in alcoholism, can produce confusion and psychotic symptoms, in addition to neurological signs. Vitamin Bsub 1sub 2 and folate deficiency may contribute symptoms of disorientation, depression or psychosis; their measurement is a part of routine dementia work-ups. Pyridoxine deficiency results in seizures, although the effects of exogenously administered pyridoxine are not clearly understood in depression and anxiety - the disorders in which it is most frequently used clinically. The use of vitamins has been most prominent in psychiatry in the treatment of schizophrenia, where large doses of nicotinic acid were initially given alone and later combined with other vitamins and minerals. Several theoretical models were described to support the use of vitamins in schizophrenia. These included: the parallels of schizophrenia to the psychiatric symptoms of pellagra; hypotheses of a defect in adrenaline metabolism; and the accumulation of psychotoxic substances which produce psychotic symptoms. Initially, positive results were reported over 30 years ago, but have not been replicated by thorough investigations. An extensive series of comprehensive placebo-controlled trials failed to show efficacy for any of the vitamin therapies tested. Although clearly less effective than antipsychotic drug

treatment, vitamin therapy is not without risks - adverse effects have been reported with nicotinic acid, pyridoxine and vitamin C. Although the possible role of vitamins has played an important part in the development of biological psychiatry, vitamin therapy is no longer extensively practised, and claims for its efficacy have not been supported by objective scientific evidence.

S-adenosyl-L-methionine (SAMe) in clinical practice: Preliminary report on 75 minor depressives

De Leo D.
University of Padua, School of Medicine, Department of Psychiatry, Padua Italy
Current Therapeutic Research - Clinical and Experimental (United States) 1985, 37/4 (658-661)

An open trial was performed on a population of 75 patients suffering from minor depression. The subjects were administered 100 mg/die of S-adenosyl-L-methionine intramuscularly for 30 days. Modifications occurring were evaluated with the Zung SelRating Depression Scale and with the Clinical Global Impression and Patient Global Impression. The trial showed SAMe to have good clinical efficacy and to be virtually devoid of side effects.

S-Adenosyl-L-Methionine (SAMe) treatment in psychogeriatry: a controlled clinical trial in depressed patients

G.Gerontol. (Italy), 1977, 25/3

The authors report some results obtained by treatment with S-Adenosyl-L-Methionine (135 mg/day given intramuscularly for 15 days) in senile depressed patients (17 subjects). The evaluation was performed using the Hamilton Rating Scale for depression (HRS) and the scale by Overall and Gorham (BPRS). The items considering the depressive state improved significantly by treatment.

A methyl donor, adenosylmethionine, in depression

Folia Neuropsychiat.(Lecce) (Italy), 1973, 16/4

Because of the excellent results obtained by Fazio et al. in depressive syndromes with S adenosyl L methionine (SAM), the same drug was administered in the present trial. It was given intravenously in doses of 45 mg per day, for periods of 10 to 20 days to 8 patients suffering from depressive syndromes. Five patients (62%) were cured. Normalization occurred rapidly (in 5 days) and appeared to be lasting (still good at followup 5 months after the end of the treatment). Since SAM readily gives off methyl groups and since it passes the blood brain barrier, it

probably influences the biochemistry of the brain, especially its catecholamine metabolism which is probably subnormal in depressive psychoses. Consequently, it may be regarded as a highly useful drug in the treatment of hypothermic syndromes; further trials on a larger scale are advocated.

Therapeutic effects and mechanism of action of S adenosyl l methionine in depressive syndromes

Fazio C, Andreoli V, Agnoli A, Casacchia M, Cerbo R
Minerva Med 1973 Apr 30;64(29):1515-29

S-adenosyl methionine (SAM) is physiologically synthesised in the CNS and present in various concentrations in the different areas of the brain. The donor substance is activated by methyls and is involved in neurotransmitter synthesis and catabolism process. SAM injected into the systemic circulation rapidly crosses the blood brain barrier and is thus a potential nerve drug in the management of depression in the present crisis surrounding neuropharmacological theory. An open and double blind clinical trial was run on 49 patients. The drug manifested a rapid and intense antidepressive action, with positive results in over 80% of cases. A specific rating scale (Hamilton's scale) for depression was used in evaluating the experiment and the effect of the drug on certain target symptoms is discussed.

Monitoring S-adenosyl-methionine blood levels and antidepressant effect

Del Vecchio M, Amati A, Vacca L, Zizolfi S
Acta Neurol (Napoli) 1980 Dec;2(6):488-95

Seven depressed inpatients, classified according to the Multi-Aspect Classification Model, were treated with S-adenosyl-methionine (SAMe), 200 mg pro die i.v. for three weeks, in a single blind trial. Blood SAMe levels were determined in samples collected in a basal condition and after drug administration on the 7th, 14th and 21st day of the treatment. Computerized spectral frequency analysis of bioelectric brain activity has been performed before and after the treatment using some geometrical spectral parameters. The Hamilton Rating Scale for Depression (HRS), Comprehensive Psychopathological Rating Scale and Zung's Scale were rated before, during and after the treatment on the days of blood collection. At the end of the treatment, the improvement, according to HRS total scores, varied from 12.8 to 42.8 per cent (mean + or - SD: 21.8 + or - 4). No side effects were noted. A negative linear correlation was found between HRS total scores and blood SAMe levels ($r = -0.3641$; $p<0.05$). EEG spectral computerized analysis shows some differences after the treatment, which might indicate that SAMe interacts with brain tissues. Further studies are required to clarify the relationship between blood SAMe levels, therapeutic response and EEG recordings.

Clinic and psychometric effects of S adenosyl methionine on chronically L Dopa treated parkinsonians

Acta Neurol. (Napoli) (Italy), 1977, 32/2 (204-217)

S adenosyl methionine was administered for 15 days i.v. by glucose, at a daily dosage of 60 mg, to 15 subjects affected by idiopathic parkinsonism in chronic treatment with L-Dopa. SAM: favors the remission of akinesia; has an antidepressive effect; increases the anxious valencies; is a manageable drug, well tolerated with secondary side effects of minute importance.

14. Diabetes

Preventative and curative options include:

Alpha lipoic acid, american ginseng, aminoguanidine, bilberry, biotin carnitine, carnosine, CoQ10, chromium, CLA, DHEA, essential fatty acids, garlic, ginkgo biloba, gymnema sylvestre, magnesium, n-acetyl-L-cysteine, niacin, silymarin, vanadyl sulphate, vitamin C, vitamin E, vitamin K.

[Antiplatelet properties of nitrogen monoxide] [Article in French]

Adrie C. Service de reanimation medicale, hopital Saint-Louis, Paris.

Arch Mal Coeur Vaiss 1996 Nov;89(11 Suppl):1527-32

Nitric (correction of nitrous) oxide (NO) plays a fundamental part in the haemostatic equilibrium between the endothelium and platelets, an equilibrium of established clinical importance in cardiovascular disease. NO stimulates the enzyme guanylate cyclase which is responsible for synthesis of GMPc, the increase of which results in platelet inhibition. Synthesis of NO may have endogenous auto or paracrine origine from platelets or endothelial cells and participates in the local regulation of platelet function in association with other products of endothelial or platelet synthesis. Exogenous administration is common in therapeutics either in molecules which release NO (nitrate derivatives, sodium nitropruside, molsidomine, etc) or by NO gas administered by inhalation. The antiplatelet effect of NO has been clearly demonstrated in vitro, in vivo or ex vivo, in animals and humans, and probably explains, at least partially, the efficacy of nitrate derivatives in ischaemic coronary artery disease. Nevertheless, the platelet inhibition observed with intravenous NO releasing drugs is associated with potentially harmful systemic hypotension. Platelet inhibition by inhalation of NO could be an alternative means of avoiding this unwanted effect.

Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes.

Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J. Beltsville Human Nutrition Research Center, U.S. Department of Agriculture, Beltsville, MD 20705-2350, USA. anderson@307.bhnrc.usda.gov

Diabetes 1997 Nov;46(11):1786-91

Chromium is an essential nutrient involved in normal carbohydrate and lipid metabolism. The chromium requirement is postulated to increase with increased glucose intolerance and diabetes. The objective of this study was to test the

hypothesis that the elevated intake of supplemental chromium is involved in the control of type 2 diabetes. Individuals being treated for type 2 diabetes (180 men and women) were divided randomly into three groups and supplemented with: 1) placebo, 2) 1.92 micromol (100 microg) Cr as chromium picolinate two times per day, or 3) 9.6 micromol (500 microg) Cr two times per day. Subjects continued to take their normal medications and were instructed not to change their normal eating and living habits. HbA1c values improved significantly after 2 months in the group receiving 19.2 pmol (1,000 microg) Cr per day and was lower in both chromium groups after 4 months (placebo, 8.5 +/- 0.2%; 3.85 micromol Cr, 7.5 +/- 0.2%; 19.2 micromol Cr, 6.6 +/- 0.1%). Fasting glucose was lower in the 19.2-micromol group after 2 and 4 months (4-month values: placebo, 8.8 +/- 0.3 mmol/l; 19.2 micromol Cr, 7.1 +/- 0.2 mmol/l). Two-hour glucose values were also significantly lower for the subjects consuming 19.2 micromol supplemental Cr after both 2 and 4 months (4-month values: placebo, 12.3 +/- 0.4 mmo/l; 19.2 micromol Cr, 10.5 +/- 0.2 mmol/l). Fasting and 2-h insulin values decreased significantly in both groups receiving supplemental chromium after 2 and 4 months. Plasma total cholesterol also decreased after 4 months in the subjects receiving 19.2 micromol/day Cr. These data demonstrate that supplemental chromium had significant beneficial effects on HbA1c, glucose, insulin, and cholesterol variables in subjects with type 2 diabetes. The beneficial effects of chromium in individuals with diabetes were observed at levels higher than the upper limit of the Estimated Safe and Adequate Daily Dietary Intake.

The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes.

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Saudi Med J 2000 Sep;21(9):831-7

OBJECTIVE: To study the effects of supplementation with organic and inorganic chromium on glucose tolerance, serum lipids, and drug dosage in type 2 diabetes patients, in the hope of finding a better and more economical method of control. METHODS: Seventy eight type 2 diabetes patients were divided randomly into two groups and given Brewer's yeast (23.3ug Cr/day), and CrCl3 (200ug Cr/day) sequentially with placebo in between, in a double blind cross-over design of four stages, each lasting 8 weeks. At the beginning and end of each stage, subjects were weighed, their dietary data and drug dosage recorded, and blood and urine samples were collected for analysis of glucose (fasting and 2 hour post 75g glucose load) fructosamine, triglycerides, total and HDL-cholesterol, and serum and urinary chromium. RESULTS: Both supplements caused a significant decrease in the means of glucose (fasting and 2 hour post glucose load), fructosamine and triglycerides. The means of HDL-cholesterol, and serum and urinary chromium were all increased. The mean drug dosage decreased slightly (and significantly in case of Glibenclamide) after both supplements and some patients no longer required insulin. No change was noted in dietary intakes or Body Mass Index. A higher percentage of subjects responded positively to

Brewer's yeast chromium, which was retained more by the body, with effects on fructosamine, triglycerides, and HDL-cholesterol maintained in some subjects when placebo followed it, and mean urinary chromium remaining significantly higher than zero time mean. CONCLUSION: Chromium supplementation gives better control of glucose and lipid variables while decreasing drug dosage in type 2 diabetes patients. A larger scale study is needed to help decide on the convenient chemical form, and dosage required to achieve optimal response.

Dehydroepiandrosterone prevents lipid peroxidation and cell growth inhibition induced by high glucose concentration in cultured rat mesangial cells.

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J Endocrinol 2000 Aug;166(2):401-6

The oxidative stress induced by high glucose concentration contributes to tissue damage associated with diabetes, including renal injury. Dehydroepiandrosterone (DHEA), the major secretory product of the human adrenal gland, has been shown to possess a multi-targeted antioxidant activity which is also effective against lipid peroxidation induced by high glucose. In this study we evaluated the effect of DHEA on the growth impairment which high glucose concentration induces in cultured rat mesangial cells. Primary cultures of rat mesangial cells were grown for 10 days in media containing either normal (i.e. 5.6 mmol/l) or high (i.e. 30 mmol/l) concentrations of glucose, without or with DHEA at different concentrations. The impairment of cell growth induced by high glucose was reversed by 100 nmol/l and 500 nmol/l DHEA, which had no effect on mesangial cells cultured in media containing glucose at the normal physiological concentration (5.6 mmol/l). In high-glucose cultured mesangial cells, DHEA also attenuated the lipid peroxidation, as measured by thiobarbituric acid reactive substances (TBARS) generation and 4-hydroxynonenal (HNE) concentration, and preserved the cellular content of reduced glutathione as well as the membrane Na+/K+ ATPase activity. The data further support the protective effect of DHEA against oxidative damage induced by high glucose concentrations, and bring into focus its possible effectiveness in preventing chronic complications of diabetes.

Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus.

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N Engl J Med 2000 May 11;342(19):1392-8

BACKGROUND: The effect of increasing the intake of dietary fiber on glycemic control in patients with type 2 diabetes mellitus is controversial. METHODS: In a

randomized, crossover study, we assigned 13 patients with type 2 diabetes mellitus to follow two diets, each for six weeks: a diet containing moderate amounts of fiber (total, 24 g; 8 g of soluble fiber and 16 g of insoluble fiber), as recommended by the American Diabetes Association (ADA), and a high-fiber diet (total, 50 g; 25 g of soluble fiber and 25 g of insoluble fiber), containing foods not fortified with fiber (unfortified foods). Both diets, prepared in a research kitchen, had the same macronutrient and energy content. We compared the effects of the two diets on glycemic control and plasma lipid concentrations. RESULTS: Compliance with the diets was excellent. During the sixth week, the high-fiber diet, as compared with the the sixth week of the ADA diet, mean daily preprandial plasma glucose concentrations were 13 mg per deciliter [0.7 mmol per liter] lower (95 percent confidence interval, 1 to 24 mg per deciliter [0.1 to 1.3 mmol per liter]; P=0.04) and mean median difference, daily urinary glucose excretion 1.3 g (0.23; 95 percent confidence interval, 0.03 to 1.83 g; P= 0.008). The high-fiber diet also lowered the area under the curve for 24-hour plasma glucose and insulin concentrations, which were measured every two hours, by 10 percent (P=0.02) and 12 percent (P=0.05), respectively. The high-fiber diet reduced plasma total cholesterol concentrations by 6.7 percent (P=0.02), triglyceride concentrations by 10.2 percent (P=0.02), and very-low-density lipoprotein cholesterol concentrations by 12.5 percent (P=0.01). CONCLUSIONS: A high intake of dietary fiber, particularly of the soluble type, above the level recommended by the ADA, improves glycemic control, decreases hyperinsulinemia, and lowers plasma lipid concentrations in patients with type 2 diabetes.

Novel lipid-lowering properties of Vaccinium myrtillus L. leaves, a traditional antidiabetic treatment, in several models of rat dyslipidaemia: a comparison with ciprofibrate.

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Thromb Res 1996 Dec 1;84(5):311-22

Vaccinium myrtillus L. (blueberry) leaf infusions are traditionally used as a folk medicine treatment of diabetes. To further define this therapeutical action, a dried hydroalcoholic extract of the leaf was administered orally to streptozotocin-diabetic rats for 4 days. Plasma glucose levels were consistently found to drop by about 26% at two different stages of diabetes. Unexpectedly, plasma triglyceride (TG) were also decreased by 39% following treatment. Subsequent to the latter observation, possible lipid-lowering properties of the extract were investigated on other models of hyperlipidaemia and ciprofibrate, a well-established hypolipidaemic drug, was used as a reference compound. Both drug reduced TG levels of rats on hyperlipidaemic diet in a dose-dependent fashion. When administered at single doses over the same experimental period, blueberry and ciprofibrate were effective in lowering TG concentrations in ethanol-treated normolipidaemic animals and in genetically hyperlipidaemic Yoshida rats. Unlike ciprofibrate, however, blueberry failed to prevent the rise in plasma TG elicited by fructose and did not affect free fatty acid levels in any of the above experimental conditions. In rats treated with Triton WR-1339, blueberry feeding

induced an hypolipidaemic activity one hour after injection but proved to be ineffective at later time points, thus suggesting that its hypolipidaemic action may reflect improved TG-rich lipoprotein catabolism. In addition, ciprofibrate and the extract were tested for antithrombotic activity using a collagen-triggered model of venous thrombosis in diabetic and Yoshida rats. Only ciprofibrate, however, significantly reduced thrombus formation in diabetics, possibly because of its effects on free fatty acid metabolism, whereas no effect was observed in Yoshida rats. In conclusion, the present findings indicate that active consituent(s) of Vaccinium myrtillus L. leaves may prove potentially useful for treatment of dyslipidaemiae associated with impaired TG-rich lipoprotein clearance.

Nitric oxide synthase: role in the genesis of vascular disease.

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Annu Rev Med 1997;48:489-509

The product of nitric oxide (NO) synthase is the most potent endogenous vasodilator known. No not only is a potent vasodilator, it also inhibits platelet adherence and aggregation, reduces adherence of leukocytes to the endothelium, and suppresses proliferation of vascular smooth muscle cells. A number of disorders are associated with reduced synthesis and/or increased degradation of vascular NO. These include hypercholesterolemia, diabetes mellitus, hypertension, and tobacco use. The endothelial dysfunction caused by these disorders contributes to the alterations in vascular function and structure observed in these conditions. A reduction in the activity of vascular NO likely plays a significant role in the development of atherosclerosis. Insights into the mechanisms by which NO production or activity is altered in these states will lead to new therapeutic strategies in the treatment of a number of vascular disorders, including hypertension, atherosclerosis, restenosis, and thrombosis.

Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation.

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Metabolism 1994 Dec;43(12):1558-62

The urinary excretion of zinc in individuals with insulin-dependent diabetes mellitus (IDDM) is approximately doubled. In the absence of a compensatory mechanism, this hyperzincuria should induce a deficient or marginal Zn status. We examined parameters of Zn status in plasma and in blood cells with respect to urinary Zn losses and Zn supplementation. We measured Zn levels in the urine, plasma, and erythrocytes of 14 IDDM subjects and 15 nondiabetics who kept dietary records for 3 consecutive days. Subsequently, six IDDM subjects and seven nondiabetics were supplemented with 50 mg Zn daily for 28 days. We measured the above parameters, as well as mononuclear leukocyte Zn (MNL-Zn)

and the plasma subfraction of albumin-bound Zn (alb-Zn). The total plasma Zn-binding capacity was also assessed. Plasma copper and erythrocyte Cu were monitored as indicators of potential Zn toxicity. Individuals with IDDM displayed the expected hyperzincuria, but had normal blood Zn parameters. Zincuria increased by a similar amount in both groups during supplementation, as did the MNL-Zn content. However, erythrocyte Zn (e-Zn) was refractory, so a trend toward lower e-Zn among IDDM subjects persisted during Zn supplementation. Hemoglobin A1c (HbA1c) increased markedly in the Zn-supplemented IDDM group. Despite their chronic hyperzincuria, individuals with IDDM appear not to be Zn-deficient. Large-dose Zn supplementation increases MNL-Zn and induces an undesirable elevation of HbA1c in all individuals. This is especially disconcerting for those with IDDM, and may reflect an exacerbation of a chronic "Zn diabetes." These data suggest a potential for toxicity from large-dose Zn supplementation.

Low-density lipoprotein postsecretory modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications: the effect of alpha-tocopherol supplementation.

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Circulation 2000 Jul 11;102(2):191-6

BACKGROUND: Although diabetes confers an increased propensity toward accelerated atherogenesis, data are lacking on monocyte activity in type 2 diabetic patients with (DM2-MV) and without (DM2) macrovascular disease compared with control subjects. Thus, we tested whether (1) postsecretory modifications of LDL (glycation and oxidation), monocyte proatherogenic activity, and circulating levels of soluble cell adhesion molecules (sCAMs) are more pronounced in DM2-MV than in DM2 and control subjects and (2) RRR-alpha-tocopherol (AT) therapy, 1200 IU/d for 3 months, has a similar effect in the 3 groups (n=25 per group). METHODS AND RESULTS: Although LDL glycation was increased in both diabetic groups compared with control subjects, AT therapy had no significant effect on glycation. AT therapy significantly decreased LDL oxidizability in all 3 groups. Diabetic monocytes released significantly more superoxide anion (O(2)(-)) and interleukin-1beta (IL-1beta) and exhibited greater adhesion to endothelium than control subjects. AT therapy significantly decreased the release of O(2)(-), IL-1beta, tumor necrosis factor-alpha, and monocyte-endothelium adhesion in all 3 groups. There was no significant difference between the 2 diabetic groups for any of the above parameters. sICAM levels were significantly elevated in both diabetic groups compared with controls. AT therapy resulted in a significant decrease in sCAMs. CONCLUSIONS: This is the first demonstration of increased IL-1beta secretion and increased adhesion of monocytes to endothelium from normotriglyceridemic diabetic subjects and of decreased monocyte activity and sCAMs with AT therapy in diabetic subjects with and without macrovasculopathy.

Diabetes-induced nitrative stress in the retina, and correction by aminoguanidine.

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J Neurochem 2002 Mar;80(5):771-9

Aminoguanidine inhibits the development of retinopathy in diabetic animals, but the mechanism remains unclear. Inasmuch as aminoguanidine is a relatively selective inhibitor of the inducible isoform of nitric oxide synthase (iNOS), we have investigated the effects of hyperglycemia on the retinal nitric oxide (NO) pathway in the presence and absence of aminoguanidine. In vivo studies utilized retinas from experimentally diabetic rats treated or without aminoguanidine for 2 months, and in vitro studies used bovine retinal endothelial cells and a transformed retinal glial cell line (rMC-1) incubated in 5 mm and 25 mm glucose with and without aminoguanidine (100 microg/mL). NO was detected as nitrite and nitrate, and nitrotyrosine and iNOS were detected using immunochemical methods. Retinal homogenates from diabetic animals had greater than normal levels of NO and iNOS (< 0.05), and nitrotyrosine was greater than normal, especially in one band immunoprecipitated from retinal homogenates. Oral aminoguanidine significantly inhibited all of these increases. Nitrotyrosine was detected immunohistochemically only in the retinal vasculature of non-diabetic and diabetic animals. Retinal endothelial and rMC-1 cells cultured in high glucose increased NO and NT, and aminoguanidine inhibited both increases in rMC-1 cells, but only NT in endothelial cells. Hyperglycemia increases NO production in retinal cells, and aminoguanidine can inhibit this abnormality. Inhibition of diabetic retinopathy by aminoguanidine might be mediated in part by inhibition of sequelae of NO production.

Magnesium and insulin-dependent diabetes mellitus.

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Diabetes Res Clin Pract 1990 Nov-Dec;10(3):203-9

There is accumulating evidence that the changes which occur in the metabolism of some micronutrients in diabetes mellitus might have a specific role in the pathogenesis and complications of this disease. Magnesium deficiency is the most evident disturbance of metal metabolism in insulin-dependent diabetes mellitus. Hypomagnesemia has been linked both to the acute metabolic and late chronic complication of diabetes. Of particular concern, is the association between hypomagnesemia and ischemic heart disease and severe retinopathy in humans with diabetes mellitus. Appropriate magnesium supplementation might prove beneficial in normalizing the low plasma and tissue magnesium levels and prevent or retard the development of vascular complications in diabetic patients.

However, well designed and documented experiments need to be performed before the rationales for such therapy are well established.

Zinc and insulin sensitivity.

Faure P, Roussel A, Coudray C, Richard MJ, Halimi S, Favier A. Laboratoire de Biochimie C, Hopital A. Michallon, Grenoble, France.

Biol Trace Elem Res 1992 Jan-Mar;32:305-10

Many studies have shown that zinc deficiency could decrease the response to insulin. In genetically diabetic animals, a low zinc status has been observed contrary to induced diabetic animals. The zinc status of human patients depends on the type of diabetes and the age. Zinc supplementation seems to have beneficial effects on glucose homeostasis. However, the mechanism of insulin resistance secondary to zinc depletion is yet unclear. More studies are therefore necessary to document better zinc metabolism in diabetes mellitus, and the antioxidant activity of zinc on the insulin receptor and the glucose transporter.

Cross-talk between iron metabolism and diabetes.

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Diabetes 2002 Aug;51(8):2348-54

Emerging scientific evidence has disclosed unsuspected influences between iron metabolism and type 2 diabetes. The relationship is bi-directional--iron affects glucose metabolism, and glucose metabolism impinges on several iron metabolic pathways. Oxidative stress and inflammatory cytokines influence these relationships, amplifying and potentiating the initiated events. The clinical impact of these interactions depends on both the genetic predisposition and the time frame in which this network of closely related signals acts. In recent years, increased iron stores have been found to predict the development of type 2 diabetes while iron depletion was protective. Iron-induced damage might also modulate the development of chronic diabetes complications. Iron depletion has been demonstrated to be beneficial in coronary artery responses, endothelial dysfunction, insulin secretion, insulin action, and metabolic control in type 2 diabetes. Here, we show that iron modulates insulin action in healthy individuals and in patients with type 2 diabetes. The extent of this influence should be tested in large-scale clinical trials, searching for the usefulness and cost-effectiveness of therapeutic measures that decrease iron toxicity. The study of individual susceptibility and of the mechanisms that influence tissue iron deposition and damage are proposed to be valuable in anticipating and treating diabetes complications.

Aminoguanidine prolongs survival in azotemic-induced diabetic rats.

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Am J Kidney Dis 1997 Aug;30(2):253-9

Toxic effects of hyperglycemia-induced advanced glycosylated end products (AGEs) may explain some vasculopathic complications of diabetes. Aminoguanidine, a known inhibitor of AGE formation, was administered by gavage to Sprague-Dawley streptozotocin-induced diabetic rats made azotemic by surgical reduction of renal mass. All rats became hyperglycemic. Renal ablation caused renal insufficiency, as evidenced by markedly reduced endogenous creatinine clearances at days 7 and 14. Aminoguanidine-treated rats had significantly (< 0.04) superior survival to that of untreated azotemic diabetic rats. We infer from the extended life in a rat model of uremia in diabetic nephropathy that aminoguanidine may prove beneficial in human diabetes.

Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress?

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Metabolism 1995 Mar;44(3):363-8

Accelerated atherosclerotic vascular disease is the leading cause of mortality in patients with diabetes mellitus. Endothelium-derived nitric oxide (NO) is a potent endogenous nitrovasodilator and plays a major role in modulation of vascular tone. Selective impairment of endothelium-dependent relaxation has been demonstrated in aortas of both nondiabetic animals exposed to elevated concentrations of glucose in vitro and insulin-dependent diabetic animals. The impaired NO release in experimentally induced diabetes may be prevented by a number of antioxidants. It has been hypothesized that oxygen-derived free radicals (OFR) generated during both glucose autoxidation and formation of advanced glycosylation end products may interfere with NO action and attenuate its vasodilatory activity. The oxidative injury may also be increased in diabetes mellitus because of a weakened defense due to reduced endogenous antioxidants (vitamin E, reduced glutathione [GSH]). A defective endothelium-dependent vascular relaxation has been found in animal models of hypertension and in hypertensive patients. An imbalance due to reduced production of NO or increased production of free radicals, mainly superoxide anion, may facilitate the development of an arterial functional spasm. Treatment with different antioxidants increases blood flow in the forearm and decreases blood pressure and viscosity in normal humans; vitamin E inhibits nonenzymatic glycosylation, oxidative stress, and red blood cell microviscosity in diabetic patients. Long-term randomized clinical trials of adequate size in secondary and primary prevention could support the free-radical hypothesis for diabetic diabetic vascular complications and the use of antioxidants to reduce the risk of coronary heart disease.

Clinical and experimental study on the long-term effect of dietary gamma-linolenic acid on plasma lipids, platelet aggregation, thromboxane formation, and prostacyclin production.

Guivernau M, Meza N, Barja P, Roman O. Department of Medicine, School of Medicine, University of Chile, Santiago.

Prostaglandins Leukot Essent Fatty Acids 1994 Nov;51(5):311-6

Effects of a dietary intake of the polyunsaturated omega-6 essential fatty acids (EFAs) linoleic and gamma-linolenic acids (GLA) on blood lipids, platelet function, and vascular prostacyclin production were studied 12 hyperlipidemic patients (doses of 3 g/day) and 12 male Wistar rats (doses of 3 mg/kg/day) for 4 months. In humans, GLA supplementation decreased plasma triglyceride (TG) levels by 48% (< 0.001) and increased HDL-cholesterol concentration by 22% (< 0.01). Total cholesterol and LDL-cholesterol levels were significantly decreased by omega-6 EFAs. Platelet aggregation induced by low concentrations of adenosine diphosphate (ADP) and epinephrine, and serum thromboxane B2 decreased by 45% both in humans and animals after GLA supplementation. Bleeding time increased 40% (p , 0.01). In rats, vascular prostacyclin production measured by radioimmunoassay of 6-keto-PGF1 alpha was enhanced by GLA intake. These effects of omega-6 EFAs may contribute to cardiovascular protection and prevention of the atherosclerotic disease.

DHEA treatment reduces fat accumulation and protects against insulin resistance in male rats.

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J Gerontol A Biol Sci Med Sci 1998 Jan;53(1):B19-24

The purpose of this study was to determine whether administration of dehydroepiandrosterone (DHEA) protects male rats against the accumulation of body fat the development of insulin resistance with advancing age. We found that supplementation of the diet with 0.3% DHEA between the ages of 5 months and approximately 25 months resulted in a significantly lower final body weight (DHEA, 593 +/- 18 g vs control, 668 +/- 12 g, < 0.02), despite no decrease in food intake. Lean body mass was unaffected by the DHEA, and the lower body weight was due to a approximately 25% reduction in body fat. The rate of glucose disposal during a euglycemic, hyperinsulinemic clamp was 30% higher in the DHEA group than in the sedentary controls due to a greater insulin responsiveness. The DHEA administration was as effective in reducing body fat content and maintaining insulin responsiveness as exercise in the form of voluntary wheel running. The DHEA had no significant effect on muscle GLUT4 content. A preliminary experiment provided evidence suggesting that muscle insulin signaling, as reflected in binding of phosphatidylinositol 3-kinase to the insulin receptor substrate-1, was enhanced in the DHEA-treated and wheel running groups as compared to controls. These results provide evidence that

DHEA, like exercise, protects against excess fat accumulation and development of insulin resistance in rats.

A possible new role for the anti-ageing peptide carnosine.

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Cell Mol Life Sci 2000 May;57(5):747-53

The naturally occurring dipeptide carnosine (beta-alanyl-L-histidine) is found in surprisingly large amounts in long-lived tissues and can delay ageing in cultured human fibroblasts. Carnosine has been regarded largely as an anti-oxidant and free radical scavenger. More recently, an anti-glycating potential has been discovered whereby carnosine can react with low-molecular-weight compounds that bear carbonyl groups (aldehydes and ketones). Carbonyl groups, arising mostly from the attack of reactive oxygen species and low-molecular-weight aldehydes and ketones, accumulate on proteins during ageing. Here we propose, with supporting evidence, that carnosine can react with protein carbonyl groups to produce protein-carbonyl-carnosine adducts ('carnosinylated' proteins). The various possible cellular fates of the carnosinylated proteins are discussed. These proposals may help explain anti-ageing actions of carnosine and its presence in non-mitotic cells of long-lived mammals.

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

Houseknecht KL, Vanden Heuvel JP, Moya-Camarena SY, Portocarrero CP, Peck LW, Nickel KP, Belury MA. Department of Animal Sciences, Purdue University, West Lafayette, IN 47907, USA.

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

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 NIDDM.

Diet, lifestyle, and the risk of type 2 diabetes mellitus in women.

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N Engl J Med 2001 Sep 13;345(11):790-7

BACKGROUND: Previous studies have examined individual dietary and lifestyle factors in relation to type 2 diabetes, but the combined effects of these factors are largely unknown. METHODS: We followed 84,941 female nurses from 1980 to 1996; these women were free of diagnosed cardiovascular disease, diabetes, and cancer at base line. Information about their diet and lifestyle was updated periodically. A low-risk group was defined according to a combination of five variables: a bodymass index (the weight in kilograms divided by the square of the height in meters) of less than 25; a diet high in cereal fiber and polyunsaturated fat and low in trans fat and glycemic load (which reflects the effect of diet on the blood glucose level); engagement in moderate-to-vigorous physical activity for at least half an hour per day; no current smoking; and the consumption of an average of at least half a drink of an alcoholic beverage per day. RESULTS: During 16 years of follow-up, we documented 3300 new cases of type 2 diabetes. Overweight or obesity was the single most important predictor of diabetes. Lack of exercise, a poor diet, current smoking, and abstinence from alcohol use were all associated with a significantly increased risk of diabetes, even after adjustment for the body-mass index. As compared with the rest of the cohort, women in the low-risk group (3.4 percent of the women) had a relative risk of diabetes of 0.09 (95 percent confidence interval, 0.05 to 0.17). A total of 91 percent of the cases of diabetes in this cohort (95 percent confidence interval, 83 to 95) could be attributed to habits and forms of behavior that did not conform to the low-risk pattern. CONCLUSIONS: Our findings support the hypothesis that the vast majority of cases of type 2 diabetes could be prevented by the adoption of a healthier lifestyle.

Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid.

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Arzneimittelforschung 1995 Aug;45(8):872-4

Insulin resistance of skeletal muscle glucose uptake is a prominent feature of Type II diabetes (NIDDM); therefore pharmacological interventions should aim to improve insulin sensitivity. Alpha-lipoic acid (CAS 62-46-4, thioctic acid, ALA), a natural occurring compound frequently used for treatment of diabetic polyneuropathy, enhances glucose utilization in various experimental models. To see whether this compound also augments insulin mediated glucose disposal in NIDDM, 13 patients received either ALA (1000 mg/Thioctacid/500 ml NaCl, n = 7) or vehicle only (500 ml NaCl, n = 6) during a glucose-clamp study. Both groups were comparable in age, body-mass index and duration of diabetes and

had a similar degree of insulin resistance at baseline. Acute parenteral administration of ALA resulted in a significant increase of insulin-stimulated glucose disposal; metabolic clearance rate (MCR) for glucose rose by about 50% (3.76 ml/kg/min = pre vs. 5.82 ml/kg/min = post, p < 0.05), whereas the control group did not show that alpha-lipoic acid increases insulin stimulated glucose disposal in NIDDM. The mode of action of ALA and its potential use as an antihyperglycemic agent require further investigation.

The antioxidant alpha-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle.

Jacob S, Streeper RS, Fogt DL, Hokama JY, Tritschler HJ, Dietze GJ, Henriksen EJ. Department of Physiology, University of Arizona College of Medicine, Tucson, AZ, USA.

Diabetes 1996 Aug;45(8):1024-9

Insulin resistance of muscle glucose metabolism is a hallmark of NIDDM. The obese Zucker (fa/fa) rat--an animal model of muscle insulin resistance--was used to test whether acute (100 mg/kg body wt for 1 h) and chronic (5-100 mg/kg for 10 days) parenteral treatments with a racemic mixture of the antioxidant alpha-lipoic acid (ALA) could improve glucose metabolism in insulin-resistant skeletal muscle. Glucose transport activity (assessed by net 2-deoxyglucose [2-DG] uptake), net glycogen synthesis, and glucose oxidation were determined in the isolated epitrochlearis muscles in the absence or presence of insulin (13.3 nmol/l). Severe insulin resistance of 2-DG uptake, glycogen synthesis, and glucose oxidation was observed in muscle from the vehicle-treated obese rats compared with muscle from vehicle-treated lean (Fa/-) rats. Acute and chronic treatments (30 mg.kg-1.day-1, a maximally effective dose) with ALA significantly (P < 0.05) improved insulin-mediated 2-DG uptake in epitrochlearis muscles from the obese rats by 62 and 64%, respectively. Chronic ALA treatment increased both insulin-stimulated glucose oxidation (33%) and glycogen synthesis (38%) and was associated with a significantly greater (21%) in vivo muscle glycogen concentration. These adaptive responses after chronic ALA administration were also associated with significantly lower (15-17%) plasma levels of insulin and free fatty acids. No significant effects on glucose transporter (GLUT4) protein level or on the activities of hexokinase and citrate synthase were observed. Collectively, these findings indicate that parenteral administration of the antioxidant ALA significantly enhances the capacity of the insulin-stimulatable glucose transport system and of both oxidative and nonoxidative pathways of glucose metabolism in insulin-resistant rat skeletal muscle.

Lipoic acid (LA) decreases protein glycation and increases (NA++K+)- and Ca++ATPases activities in high glucose (G)-treated red blood cells (RBC)

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Free Radical Biol. Med. 1998; 25: S94 (Abstr. 268)

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na+ + K+)-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the (Na+ + K+)- and Ca++-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R sterioisomers) in a shaking water bath at 37°C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na+ + K+)- and Ca++-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na+ + K+)- and Ca++-ATPases in high glucose- treated RBC. There were no differences in lipid peroxidation, GHb and (Na+ + K+)- and Ca++-ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na+ + K+)- and Ca++-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or inhibit the development of neuropathy in diabetes.

Lipoic acid decreases lipid peroxidation and protein glycosylation and increases (Na(+) + K(+))- and Ca(++)-ATPase activities in high glucose-treated human erythrocytes.

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Free Radic Biol Med 2000 Dec;29(11):1122-8

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na(+) + K(+))-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the (Na(+) + K(+))- and Ca(++)-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R sterioisomers) in a shaking water bath at 37 degrees C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na(+) + K(+))- and Ca(++)-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na(+) + K(+))- and Ca(++)-ATPases in high glucose- treated RBC. There were no differences in lipid peroxidation, GHb and (Na(+) + K(+))- and Ca(++)-

ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na(+) + K(+))- and Ca(++)-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or inhibit the development of neuropathy in diabetes.

A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes.

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J Am Coll Nutr 2001 Aug;20(4):327-36

OBJECTIVES: These studies investigated the ability of a hydroxychalcone from cinnamon to function as an insulin mimetic in 3T3-LI adipocytes. METHODS: Comparative experiments were performed with the cinnamon methylhydroxychalcone polymer and insulin with regard to glucose uptake, glycogen synthesis. phosphatidylinositol-3-kinase dependency, glycogen synthase activation and glycogen synthase kinase-3beta activity. The phosphorylation state of the insulin receptor was also investigated. RESULTS: MHCP treatment stimulated glucose uptake and glycogen synthesis to a similar level as insulin. Glycogen synthesis was inhibited by both wortmannin and LY294002, inhibitors directed against the PI-3-kinase. In addition, MHCP treatment activated glycogen synthase and inhibited glycogen synthase kinase-3beta activities, known effects of insulin treatment. Analysis of the insulin receptor demonstrated that the receptor was phosphorylated upon exposure to the MHCP. This supports that the insulin cascade was triggered by MHCP. Along with comparing MHCP to insulin, experiments were done with MHCP and insulin combined. The responses observed using the dual treatment were greater than additive, indicating synergism between the two compounds. CONCLUSION: Together, these results demonstrate that the MHCP is an effective mimetic of insulin. MHCP may be useful in the treatment of insulin resistance and in the study of the pathways leading to glucose utilization in cells.

Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity.

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Diabetes 1999 Dec;48(12):2398-406

Oxidative stress is produced under diabetic conditions and possibly causes various forms of tissue damage in patients with diabetes. The aim of this study was to examine the involvement of oxidative stress in the progression of pancreatic beta-

cell dysfunction in type 2 diabetes and to evaluate the potential usefulness of antioxidants in the treatment of type 2 diabetes. We used diabetic C57BL/KsJ-db/db mice, in whom antioxidant treatment (N-acetyl-L-cysteine [NAC], vitamins C plus E, or both) was started at 6 weeks of age; its effects were evaluated at 10 and 16 weeks of age. According to an intraperitoneal glucose tolerance test, the treatment with NAC retained glucose-stimulated insulin secretion and moderately decreased blood glucose levels. Vitamins C and E were not effective when used alone but slightly effective when used in combination with NAC. No effect on insulin secretion was observed when the same set of antioxidants was given to nondiabetic control mice. Histologic analyses of the pancreases revealed that the beta-cell mass was significantly larger in the diabetic mice treated with the antioxidants than in the untreated mice. As a possible cause, the antioxidant treatment suppressed apoptosis in beta-cells without changing the rate of beta-cell proliferation, supporting the hypothesis that in chronic hyperglycemia, apoptosis induced by oxidative stress causes reduction of beta-cell mass. The antioxidant treatment also preserved the amounts of insulin content and insulin mRNA, making the extent of insulin degranulation less evident. Furthermore, expression of pancreatic and duodenal homeobox factor-1 (PDX-1), a beta-cell-specific transcription factor, was more clearly visible in the nuclei of islet cells after the antioxidant treatment. In conclusion, our observations indicate that antioxidant treatment can exert beneficial effects in diabetes, with preservation of in vivo beta-cell function. This finding suggests a potential usefulness of antioxidants for treating diabetes and provides further support for the implication of oxidative stress in beta-cell dysfunction in diabetes.

Lipoic acid acutely induces hypoglycemia in fasting nondiabetic and diabetic rats.

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Metabolism 1999 Apr;48(4):504-10

Lipoic acid (LA) is a unique antioxidant that increases peripheral glucose utilization in diabetic patients. This study was conducted to investigate whether the inhibition of glucose production could be an additional mechanism for the action of LA. Intravenous (i.v.) LA injection (100 or 60 mg/kg body weight) to fasting nondiabetic or streptozotocin (STZ)-induced diabetic rats caused a rapid reduction in blood glucose with no effect on circulating insulin levels. In vivo conversion of fructose to glucose was not inhibited by LA, whereas the gluconeogenesis flux from alanine was completely prevented. Reduced liver pyruvate carboxylase (PC) activity in vivo is suggested by the finding that LA induced a decrease in liver coenzyme A (CoA) content (44% and 28% reduction in nondiabetic and diabetic rats, respectively, compared with vehicle-treated animals) and liver acetyl CoA content (80% and 67% reduction in nondiabetic and diabetic rats, respectively). A reduction in plasma free carnitine (42% and 22% in nondiabetic and diabetic rats, respectively) was observed in LA-treated animals, and acylcarnitine levels were increased twofold. This could be attributed

to elevated levels of C16 and C18 acylcarnitine, without a detectable accumulation of lipoylcarnitine. Under such conditions, a significant increase in the plasma free fatty acid (FFA) concentration (204% in nondiabetic and 151% in diabetic animals) with no elevation in beta-hydroxybutyrate levels was noted. In conclusion, this study suggests that short-term administration of LA at high dosage to normal and diabetic rats causes an inhibition of gluconeogenesis secondary to an interference with hepatic fatty acid oxidation. This may render LA an antihyperglycemic agent for the treatment of diabetic subjects, who display glucose overproduction as a major metabolic abnormality.

Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes.

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Int J Dev Neurosci 1999 Dec;17(8):765-75

Dehydroepiandrosterone (DHEA) is a native neurosteroid with immunomodulating activity. DHEA effectively protects animals from several viral, bacterial and parasitic infections and it was suggested that its age-associated decline is related with immunosenescence. In the present study we examined the ability of DHEA to inhibit the production of inflammatory mediators by mycoplasma-stimulated glial cells and to change the course of acute central nervous system (CNS) inflammatory disease in vivo. Addition of DHEA (10 microg/ml) markedly inhibited tumor necrosis factor alpha (TNFalpha) and interleukin-6 (IL-6) production (98 and 95%, respectively), whereas nitric oxide (NO) and prostaglandin E2 (PGE2) production was not affected. However, daily administration of 0.5 mg DHEA to mice or 5 mg to rats did not change the clinical outcome of experimental autoimmune encephalomyelitis (EAE).

Biotin for diabetic peripheral neuropathy.

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Biomed Pharmacother 1990;44(10):511-4

Biotin in high doses was given for 1-2 years to three diabetic patients suffering from severe diabetic peripheral neuropathy. Within 4-8 weeks there was a marked improvement in clinical and laboratory findings. It is suggested that in diabetes may exist a deficiency, inactivity or unavailability of Biotin, resulting in disordered activity of biotin-dependent enzyme, pyruvate carboxylase, leading to accumulation of pyruvate and/or depletion of aspartate, both of which play a significant role in nervous system metabolism. Based on our good results, regular biotin administration could be suggested for every diabetic patient for the prevention and management of peripheral neuropathy although extensive randomised clinical trials are required.

Activation of acetyl-CoA carboxylase by a glutamate- and magnesium-sensitive protein phosphatase in the islet beta-cell.

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Diabetes 2001 Jul;50(7):1580-7

Acetyl-CoA carboxylase (ACC) catalyzes the formation of malonyl-CoA, a precursor in the biosynthesis of long-chain fatty acids, which have been implicated in physiological insulin secretion. The catalytic function of ACC is regulated by phosphorylation (inactive)-dephosphorylation (active). In this study we investigated whether similar regulatory mechanisms exist for ACC in the pancreatic islet beta-cell. ACC was quantitated in normal rat islets, human islets, and clonal beta-cells (HIT-15 or INS-1) using a [(14)C]bicarbonate fixation assay. In the beta-cell lysates, ACC was stimulated by magnesium in a concentration-dependent manner. Of all the dicarboxylic acids tested, only glutamate, albeit ineffective by itself, significantly potentiated magnesium-activated ACC in a concentration-dependent manner. ACC stimulation by glutamate and magnesium was maximally demonstrable in the cytosolic fraction; it was markedly reduced by okadaic acid (OKA) in concentrations (<50 nmol/l) that inhibited protein phosphatase 2A (PP2A). Furthermore, pretreatment of the cytosolic fraction with anti-PP2A serum attenuated the glutamate- and magnesium-mediated activation of ACC, thereby suggesting that ACC may be regulated by an OKA-sensitive PP2A-like enzyme. Streptavidin-agarose chromatography studies have indicated that glutamate- and magnesium-mediated effects on ACC are attributable to activation of ACC's dephosphorylation; this suggests that the stimulatory effects of glutamate and magnesium on ACC might involve activation of an OKA-sensitive PP2A-like enzyme that dephosphorylates and activates ACC. In our study, 5-amino-imidazolecarboxamide (AICA) riboside, a stimulator of AMP kinase, significantly inhibited glucose-mediated activation of ACC and insulin secretion from isolated beta-cells. Together, our data provide evidence for a unique regulatory mechanism for the activation of ACC in the pancreatic beta-cell, leading to the generation of physiological signals that may be relevant for physiological insulin secretion.

C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease.

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Am J Cardiol 2001 Nov 15;88(10):1139-42

The acute-phase reactant C-reactive protein (CRP) has emerged as an independent risk factor for coronary artery disease. Experimental and clinical studies provide evidence of anti-inflammatory effects of n-3 polyunsaturated fatty acids (PUFA)

derived from fish. We have studied the effect of marine n-3 PUFA on CRP levels in 269 patients referred for coronary angiography because of clinical suspicion of coronary artery disease. All patients filled out a food questionnaire regarding fish intake. The n-3 PUFA content of granulocyte membranes was determined and the concentration of CRP in serum was measured using a highly sensitive assay. The results were related to angiographic findings. CRP was significantly higher in patients with significant coronary stenoses than in those with no significant angiographic changes (p <0.001), but the CRP levels were not associated with the number of diseased vessels. Subjects with CRP levels in the lower quartile had a significantly higher content of docosahexaenoic acid (DHA) in granulocytes than subjects with CRP levels in the upper quartile (p = 0.02), and in a multivariate linear regression analysis, DHA was independently correlated to CRP (R(2) = 0.179; p = 0.003). The inverse correlation between CRP and DHA may reflect an anti-inflammatory effect of DHA in patients with stable coronary artery disease and suggest a novel mechanism by which fish consumption may decrease the risk of coronary artery disease.

Therapeutic evaluation of the effect of biotin on hyperglycemia in patients with non-insulin dependent diabetes mellitus.

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Journal of Clinical Biochemistry and Nutrition 1993 14 (3): p 211-218

The therapeutic efficacy of biotin was evaluated in 43 patients with non-insulin dependent diabetes mellitus. The serum biotin concentration in the patients was significantly lower than that in the 64 healthy control subjects and inversely correlated with the fasting blood glucose level. The oral administration of biotin, 9 mg daily, corrected the hyperglycemia in the patients with no change in their serum insulin level. The serum levels of pyruvate and lactate decreased to their normal ranges after the administration. These observations suggest that the biotin administration ameliorates abnormal glucose metabolism in diabetic patients, presumably by enhancing the activity of the biotin-dependent enzyme, pyruvate carboxylase, with a subsequent promotion of glucose utilization for the entry into the tricarboxylic acid cycle. The administration also enhanced the response to glibenclamide in patients who had been resistant to the agent, suggesting a significant increase in the potency of the endogenous insulin action. The result demonstrates that biotin administration is effective for the treatment of the patients. Neither a relapse of clinical symptoms nor an occurrence of undesirable side effects has been observed.

Diabetic cardiomyopathy and carnitine deficiency.

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J Diabetes Complications 1999 Mar-Apr;13(2):86-90

This study was designed to study the pathogenesis of cardiomyopathy in animals with longstanding (6 months) diabetes mellitus. Male Wistar rats were made diabetic by the injection of streptozotocin (35 mg/kg) intraperitoneal at 6 months of age. Myocardial contractility was evaluated at 1 year of age by an echocardiogram. Blood was collected at that time to measure blood glucose and hemoglobin A1c as an indicator of metabolic control. Serum carnitine was also measured on the same sample to evaluate the availability of this substance so essential for fatty acid metabolism in the myocardium. Myocardial anatomy was evaluated by both light and electron microscopy after the animals had diabetes for 6 months. It was found that the left ventricular volume was greater at the end of systole and diastole. There was the suggestion of left ventricular fractional shortening and calculated reduced ejection fraction indicating decreased contractility consistent with cardiomyopathy. The hearts had no evidence of coronary vascular occlusion, and the serum cholesterol was normal. Myocardial ultrastructure revealed abnormal-appearing mitochondria consistent with carnitine deficiency. Serum and myocardial carnitine levels in the animals with diabetes and reduced myocardial function were low. Carnitine levels and metabolism could be important in the pathogenesis of diabetic cardiomyopathy.

Can correction of sub-optimal coenzyme Q status improve beta-cell function in type II diabetics?

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Med Hypotheses 1999 May;52(5):397-400

A stimulus to mitochondrial respiratory activity is a crucial component of the signal transduction mechanism whereby increased plasma glucose evokes insulin secretion by beta-cells. Efficient function of the glycerol-3-phosphate shuttle is important in this regard, and the rate-limiting enzyme in this shuttle--the mitochondrial glycerol-3-phosphate dehydrogenase (G3PD)--is underexpressed in the beta cells of human type II diabetics as well of rodents that are models for this disorder. Suboptimal tissue levels of coenzyme Q10 (CoQ) could be expected to further impair G3PD activity. Clinical reports from Japan suggest that supplemental CoQ may often improve beta-cell function and glycemic control in type II diabetics. Thus, it is proposed that correction of suboptimal CoQ status, by aiding the efficiency of G3PD and of respiratory chain function, will improve the glucose-stimulated insulin secretion of diabetic beta-cells.

Toward a wholly nutritional therapy for type 2 diabetes.

McCarty MF. Helicon Foundation, San Diego, CA, USA.

Med Hypotheses 2000 Mar;54(3):483-7

It may now be feasible to target specific supplemental nutrients to each of the key dysfunctions which conspire to maintain hyperglycemia in type 2 diabetes:

bioactive chromium for skeletal muscle insulin resistance, conjugated linoleic acid for adipocyte insulin resistance, high-dose biotin for excessive hepatic glucose output, and coenzyme Q(10) for beta cell failure. Nutritional strategies which disinhibit hepatic fatty acid oxidation (involving hydroxycitrate, carnitine, pyruvate, and other adjuvants) may likewise prove beneficial - in the short term, by decreasing serum free fatty acids and, in the longer term, by promoting regression of visceral obesity. The nutrients and food factors recommended here appear to be safe and well tolerated, and thus may have particular utility for diabetes prevention.

Effects of dietary supplementation of alpha-lipoic acid on early glomerular injury in diabetes mellitus.

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J Am Soc Nephrol 2001 Jan;12(1):124-33

Antioxidants, in particular vitamin E (VE), have been reported to protect against diabetic renal injury. alpha-Lipoic acid (LA) has been found to attenuate diabetic peripheral neuropathy, but its effects on nephropathy have not been examined. In the present study, parameters of glomerular injury were examined in streptozotocin diabetic rats after 2 mo on unsupplemented diets and in diabetic rats that received the lowest daily dose of dietary LA (30 mg/kg body wt), VE (100 IU/kg body wt), or vitamin C (VC; 1 g/kg body wt), which detectably increased the renal cortical content of each antioxidant. Blood glucose values did not differ among the diabetic groups. At 2 mo, inulin clearance, urinary albumin excretion, fractional albumin clearance, glomerular volume, and glomerular content of immunoreactive transforming growth factor-beta (TGF-beta) and collagen alpha1 (IV) all were significantly increased in unsupplemented D compared with age-matched nondiabetic controls. With the exception of inulin clearance, LA prevented or significantly attenuated the increase in all of these glomerular parameters in D, as well as the increases in renal tubular cell TGF-beta seen in D. At the dose used, VE reduced inulin clearance in D to control levels but failed to alter any of the other indices of glomerular injury or to suppress renal tubular cell TGF-beta in D. VC suppressed urinary albumin excretion, fractional albumin clearance, and glomerular volume but not glomerular or tubular TGF-beta or glomerular collagen alpha1 (IV) content. LA but not VE or VC significantly increased renal cortical glutathione content in D. These data indicate that LA is effective in the prevention of early diabetic glomerular injury and suggest that this agent may have advantages over high doses of either VE or VC.

Effect of eicosapentaenoic acid ethyl ester v. oleic acid-rich safflower oil on insulin resistance in type 2 diabetic model rats with hypertriacylglycerolaemia.

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Br J Nutr 2002 Feb;87(2):157-62

The purpose of the present study was to test whether hyperlipidaemia and insulin resistance in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats can be improved by dietary supplementation with purified eicosapentaenoic acid (EPA) or oleic acid (OA). Male OLETF rats were fed powdered chow (510 g fat/kg) alone (n 8) or chow supplemented with 10 g EPA- (n 8) or OA- (n 8) rich oil/kg per d from 5 weeks until 30 weeks of age. An oral glucose tolerance test and hyperinsulinaemic euglycaemic clamp was performed at 25 and 30 weeks of age. EPA supplementation resulted in significantly (P<0.05) reduced plasma lipids, hepatic triacylglycerols, and abdominal fat deposits, and more efficient in vivo glucose disposal compared with OA supplementation and no supplementation. OA supplementation was associated with significantly increased insulin response to oral glucose compared with EPA supplementation and no supplementation. Inverse correlation was noted between glucose uptake and plasma triacylglycerol levels (r -086, P<0.001) and abdominal fat volume (r -0.80, P<0.001). The result of oral glucose tolerance test study showed that the rats fed EPA tended to improve glucose intolerance, although this was not statistically significant. Levels of plasma insulin at 60 min after glucose was significantly increased in rats fed OA compared with the other two groups. The results indicate that long-term feeding of EPA might be effective in preventing insulin resistance in diabetes-prone rats, at least in part, due to improving hypertriacylglycerolaemia.

L-carnitine improves glucose disposal in type 2 diabetic patients.

Mingrone G, Greco AV, Capristo E, Benedetti G, Giancaterini A, De Gaetano A, Gasbarrini G. Istituto di Medicina Interna, Catholic University, Rome, Italy.

J Am Coll Nutr 1999 Feb;18(1):77-82

OBJECTIVE: Aim of the present study is to evaluate the effects of L-carnitine on insulin-mediated glucose uptake and oxidation in type II diabetic patients and compare the results with those in healthy controls. DESIGN: Fifteen type II diabetic patients and 20 healthy volunteers underwent a short-term (2 hours) euglycemic hyperinsulinemic clamp with simultaneous constant infusion of L-carnitine (0.28 micromole/kg bw/minute) or saline solution. Respiratory gas exchange was measured by an open-circuit ventilated hood system. Plasma glucose, insulin, non-esterified fatty acids (NEFA) and lactate levels were analyzed. Nitrogen urinary excretion was calculated to evaluate protein oxidation. RESULTS: Whole body glucose uptake was significantly (p<0.001) higher with L-carnitine than with saline solution in the two groups investigated (48.66+/-4.73 without carnitine and 52.75+/-5.19 micromoles/kg(ffm)/minute with carnitine in healthy controls, and 35.90+/-5.00 vs. 38.90+/-5.16 micromoles/kg(ffm)/minute in diabetic patients). Glucose oxidation significantly increased only in the diabetic group (17.61+/-3.33 vs. 16.45+/-2.95 micromoles/kg(ffm)/minute, p<0.001). On the contrary, glucose storage increased in both groups (controls: 26.36+/-3.25 vs. 22.79+/-3.46 micromoles/kg(ffm)/minute, p<0.001; diabetics: 21.28+/-3.18 vs. 19.66+/-3.04

micromoles/kg(ffm)/minute, p<0.001). In type II diabetic patients, plasma lactate significantly decreased during L-carnitine infusion compared to saline, going from the basal period to the end-clamp period (0.028+/-0.0191 without carnitine and 0.0759+/-0.0329 with carnitine, p<0.0003). CONCLUSIONS: L-carnitine constant infusion improves insulin sensitivity in insulin resistant diabetic patients; a significant effect on whole body insulin-mediated glucose uptake is also observed in normal subjects. In diabetics, glucose, taken up by the tissues, appears to be promptly utilized as fuel since glucose oxidation is increased during L-carnitine administration. The significantly reduced plasma levels of lactate suggest that this effect might be exerted through the activation of pyruvate dehydrogenase, whose activity is depressed in the insulin resistant status.

Polyol pathway hyperactivity is closely related to carnitine deficiency in the pathogenesis of diabetic neuropathy of streptozotocin-diabetic rats.

Nakamura J, Koh N, Sakakibara F, Hamada Y, Hara T, Sasaki H, Chaya S, Komori T, Nakashima E, Naruse K, Kato K, Takeuchi N, Kasuya Y, Hotta N. The Third Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan.

J Pharmacol Exp Ther 1998 Dec;287(3):897-902

To investigate the relationship between polyol pathway hyperactivity and altered carnitine metabolism in the pathogenesis of diabetic neuropathy, the effects of an aldose reductase inhibitor, [5-(3-thienyl) tetrazol-1-yl]acetic acid (TAT), and a carnitine analog, acetyl-L-carnitine (ALC), on neural functions and biochemistry and hemodynamic factors were compared in streptozotocin-diabetic rats. Significantly delayed motor nerve conduction velocity, decreased R-R interval variation, reduced sciatic nerve blood flow and decreased erythrocyte 2, 3-diphosphoglycerate concentrations in diabetic rats were all ameliorated by treatment with TAT (administered with rat chow containing 0.05% TAT, approximately 50 mg/kg/day) or ALC (by gavage, 300 mg/kg/day) for 4 weeks. Platelet hyperaggregation activity in diabetic rats was diminished by TAT but not by ALC. TAT decreased sorbitol accumulation and prevented not only myo-inositol depletion but also free-carnitine deficiency in diabetic nerves. On the other hand, ALC also increased the myo-inositol as well as the free-carnitine content without affecting the sorbitol content. These observations suggest that there is a close relationship between increased polyol pathway activity and carnitine deficiency in the development of diabetic neuropathy and that an aldose reductase inhibitor, TAT, and a carnitine analog, ALC, have therapeutic potential for the treatment of diabetic neuropathy.

Metabolism and actions of dehydroepiandrosterone in humans.

Nestler JE, Clore JN, Blackard WG. Division of Endocrinology and Metabolism, Medical College of Virginia/Virginia Commonwealth University, Richmond, VA 23298-0111.

J Steroid Biochem Mol Biol 1991;40(4-6):599-605

Dehydroepiandrosterone (3 beta-hydroxy-5-androsten-17-one; DHA) and DHA-sulfate are abundantly produced adrenal steroids, whose serum concentrations exceed those of other adrenal steroids. Serum concentrations of DHA and DHA-sulfate, in contrast to other adrenal steroids, exhibit a progressive age-related decline. The mechanism(s) for this selective decline in serum DHA and DHA-sulfate levels and the biologic function of these steroids remain unknown. Studies examining insulin's regulation of adrenal androgens are reviewed. These studies show that experimentally-induced hyperinsulinemia lowers serum DHA and DHA-sulfate levels, and suggest that insulin reduces serum concentrations of these steroids by inhibiting production rather than by increasing clearance. Studies examining the actions of short-term pharmacologic DHA administration to young nonobese and obese men are also reviewed. These studies suggest that DHA may possess hypolipidemic and, possibly, anti-obesity properties. They have failed, however, to demonstrate any effect of DHA on tissue insulin sensitivity.

Dietary magnesium supplements improve B-cell response to glucose and arginine in elderly non-insulin dependent diabetic subjects.

Paolisso G, Passariello N, Pizza G, Marrazzo G, Giunta R, Sgambato S, Varricchio M, D'Onofrio F. Institute di Gerontalogia e Geriateria, Napoli, Italy.

Acta Endocrinol (Copenh) 1989 Jul;121(1):16-20

Hypomagnesemia and low erythrocyte magnesium content are both common findings in non-insulin-dependent diabetic subjects. Moreover, intracellular magnesium may play a crucial role in modulating B-cell response to glucose by interfering with potassium permeability. Eight elderly, moderately obese, non-insulin-dependent diabetic subjects were treated with either magnesium supplementation (3 g/day) to the diet or placebo. Both treatment schemes lasted 4-weeks and were separated by a 'wash-out' of 3 weeks. At the end of each treatment period, in glucose test (0.33 g/kg for 3 min) and an iv arginine (5 g) test were performed to determine the B-and A-cell responses. Dietary magnesium supplementation vs placebo produced a slight but significant decrease in basal plasma glucose (8.6 +/- 0.3 vs 8.0 +/- 0.1 mmol/l, p less than 0.05) and an increase in acute insulin response after iv glucose (3.7 +/- 2.3 vs - 14.7 +/- 0.9 pmol.l 1. (10 min)-1, p less than 0.01) and after iv arginine (151 +/- vs 81 +/- 15 pmol.l-1. (10 min)-1, p less than 0.01), respectively. Plasma glucagon levels were unaffected by chronic dietary magnesium supplementation as well under basal conditions as in response to arginine. Net increase in acute insulin response after iv glucose and after iv arginine was significantly correlated to the net increase in erythrocyte magnesium content after dietary magnesium supplementation. We conclude that magnesium administration may be a useful adjuvant to the classic hypoglycemic agents in the treatment of non-insulin-dependent diabetic subjects.

Daily magnesium supplements improve glucose handling in elderly subjects.

Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesauro P, Varricchio M, D'Onofrio F. Department of Geriatric Medicine and Metabolic Diseases, 1st Medical School, University of Naples, Italy.

Am J Clin Nutr 1992 Jun;55(6):1161-7

We demonstrated similar plasma concentrations and urinary losses but lower erythrocyte magnesium concentrations (2.18 +/- 0.04 vs 1.86 +/- 0.03 mmol/L, P less than 0.01) in twelve aged (77.8 +/- 2.1 y) vs 25 young (36.1 +/- 0.4 y), nonobese subjects. Subsequently, aged subjects were enrolled in a double-blind, randomized, crossover study in which placebo (for 4 wk) and chronic magnesium administration (CMA) (4.5 g/d for 4 wk) were provided. At the end of each treatment period an intravenous glucose tolerance test (0.33 g/kg body wt) and a euglycemic glucose clamp with simultaneous [D-3H]glucose infusion and indirect calorimetry were performed. CMA vs placebo significantly increased erythrocyte magnesium concentration and improved insulin response and action. Net increase in erythrocyte magnesium significantly and positively correlated with the decrease in erythrocyte membrane microviscosity and with the net increase in both insulin secretion and action. In aged patients, correction of a low erythrocyte magnesium concentration may allow an improvement of glucose handling.

Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients.

Paolisso G, D'Amore A, Giugliano D, Ceriello A, Varricchio M, D'Onofrio F. Department of Geriatric Medicine and Metabolic Diseases, First Medical School, University of Naples, Italy.

Am J Clin Nutr 1993 May;57(5):650-6

Ten control (healthy) subjects and 15 non-insulin-dependent diabetics underwent an oral glucose-tolerance test and a euglycemic hyperinsulinemic glucose clamp before and after vitamin E supplementation (900 mg/d for 4 mo). In control subjects (placebo-treated vs vitamin E-supplemented subjects, respectively) vitamin E reduced the area under the curve for glucose (344 +/- 21 vs 287 +/- 13 mmol.L-1 x min-1; P < 0.05) and increased total body glucose disposal (39.0 +/- 0.3 vs 47.6 +/- 0.4 mumol.kg lean body mass-1 x min-1; P < 0.05) and non-oxidative glucose metabolism (23.4 +/- 0.2 vs 30.8 +/- 0.3 mumol.kg lean body mass-1 x min-1; P < 0.05). In diabetics (placebo-treated vs vitamin E-supplemented subjects, respectively) vitamin E supplementation reduced glucose area under the curve (614 +/- 129 vs 544 +/- 98 mmol.L-1 x min-1; P < 0.03) and increased glucose disappearance (19.4 +/- 0.4 vs 26.4 +/- 0.7 mumol.kg lean body mass-1.min-1; P < 0.03), total glucose disposal (19.0 +/- 0.7 vs 28.1 +/- 0.4 mumol.kg lean body mass-1 x min-1; P < 0.02), and nonoxidative glucose metabolism (8.5 +/- 0.3 vs 13.9 +/- 0.3 mumol.kg lean body mass-1 x min-1; P < 0.02). Therefore we conclude that administration of pharmacologic doses of vitamin E is a useful tool to reduce oxidative stress and improve insulin action.

In experimental diabetes the decrease in the eye of lens carnitine levels is an early important and selective event.

Pessotto P, Liberati R, Petrella O, Romanelli L, Calvani M, Peluso G. Research, Sigma-Tau S.p.A., Pomezia, Rome, Italy.

Exp Eye Res 1997 Feb;64(2):195-201

Carnitine is present in the eye tissues of the rabbit and the highest concentration is found in the lens. In streptozotocin-diabetic rats, the carnitine loss of the lens is an initial and important event. At 8 days after the induction of diabetes, the carnitine content in the rat lens was reduced by 63% compared to control. The loss of lens carnitine continued at 15 and 45 days after the induction. Total carnitine level in the serum was diminished by 15 days, and the reduction in percentage term was much lower in comparison to the loss of lens carnitine. In the rabbit after alloxan-diabetes induction, there is an extensive loss of carnitine in the lens: -85% after 4 months. The carnitine levels in the other eye tissues seem substantially unaffected. The loss of lens carnitine was present even with an inconsistent hyperglycaemia. No difference was found in serum carnitine levels between controls and alloxan-treated rabbits. The role of carnitine in lens is still unclear, but its loss may be related to the appearance of cataract. A derivative of carnitine, acetylcarnitine, might prevent the processes involved in the formation of cataracts by a pharmacological action, as has been shown for aspirin.

Effects of coenzyme Q10 treatment on antioxidant pathways in normal and streptozotocin-induced diabetic rats.

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J Biochem Mol Toxicol 2001;15(1):41-6

Coenzyme Q10 is an endogenous lipid soluble antioxidant. Because oxidant stress may exacerbate some complications of diabetes mellitus, this study investigated the effects of subacute treatment with exogenous coenzyme Q10 (10 mg/kg/day, i.p. for 14 days) on tissue antioxidant defenses in 30-day streptozotocin-induced diabetic Sprague-Dawley rats. Liver, kidney, brain, and heart were assayed for degree of lipid peroxidation, reduced and oxidized glutathione contents, and activities of catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. All tissues from diabetic animals exhibited increased oxidative stress and disturbances in antioxidant defense when compared with normal controls. Treatment with the lipophilic compound coenzyme Q10 reversed diabetic effects on hepatic glutathione peroxidase activity, on renal superoxide dismutase activity, on cardiac lipid peroxidation, and on oxidized glutathione concentration in brain. However, treatment with coenzyme Q10 also exacerbated the increase in cardiac catalase activity, which was already elevated by diabetes, further decreased hepatic glutathione reductase activity, augmented the increase in hepatic lipid peroxidation, and further increased glutathione peroxidase activity in the heart and brain of diabetic animals. Subacute dosing with coenzyme Q10

ameliorated some of the diabetes-induced changes in oxidative stress. However, exacerbation of several diabetes-related effects was also observed.

The influence of zinc supplementation on glucose homeostasis in NIDDM.

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Diabetes Res 1989 Jun;11(2):73-9

Decreased serum zinc levels and hyperzincuria occur in some non-insulin dependent diabetic subjects (NIDDM). Zinc deficiency was demonstrated in various tissues of animal models for NIDDM. Serum zinc and 24-hr urine zinc of subjects with NIDDM were compared with that of age- and sex-matched healthy volunteers. Zincuria was significantly increased in the diabetic group. Thirteen diabetic subjects with hyperzincuria and hypozincemia were supplemented with zinc sulfate 220 mg x 3/day for 7-8 weeks. At the end of the study, glucose disposal (evaluated by kg) decreased significantly from 0.562 +/- 0.03 to 0.414 +/- 0.05 (p less than 0.05) and fasting glucose and fructosamine were significantly increased from 177 +/- 10 mg/dl to 207 +/- 15 mg/dl (p less than 0.05) and from 2.7 +/- 0.2% to 3.2 +/- 0.28% (p less than 0.05), respectively. T-lymphocyte response to phytohemagglutinin was increased significantly. We conclude that zinc supplementation to NIDD patients with hypozincemia and hyperzincemia might aggravate their glucose intolerance. More accurate methods to assess zinc deficiency in NIDD patients is needed to justify the supplementation of zinc in these patients.

Relationship between acute insulin response and vitamin K intake in healthy young male volunteers.

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Diabetes Nutr Metab 1999 Feb;12(1):37-41

To evaluate the effects of vitamin K (VK) on pancreatic function, especially on acute insulin response, 25 healthy young male volunteers were given an oral load of 75 g of glucose, and their mean daily VK intake was estimated by a one-week food check list. After excluding low (<20) and high (> or =25) body mass index (BMI) subjects, the remaining 16 participants were divided into three semi-equal groups according to VK intake. Blood VK status of the low VK intake group tended to be poorer than that of the high intake group (median of 5 samples: prothrombin time; 12.5 vs 12.2s and protein-induced VK absence-factor-II; 23 vs 15 mAU/ml), but fasting plasma glucose status was not markedly different between both groups: [plasma glucose (PG); 87 vs 86 mg/dl, immunoreactive insulin (IRI); 6.7 vs 5.3 microU/ml, HbA1c; 4.8 vs 4.9%]. However, at 30 min after glucose loading, PG of the low VK intake group tended to be higher than those of the high intake group (160 vs 145 mg/dl) and IRI was lower (36.1 vs 52.3 microU/ml). Insulinogenic index (incremental

IRI/incremental PG, 0-30 min) of the low VK intake group was significantly lower than that of the high intake group (0.4 vs 0.9). These results suggested that VK may play an important role on the acute insulin response in glucose tolerance.

Vitamin C and hyperglycemia in the European Prospective Investigation into Cancer--Norfolk (EPIC-Norfolk) study: a population-based study.

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Diabetes Care 2000 Jun;23(6):726-32

OBJECTIVE: To examine the cross-sectional association between plasma vitamin C, self-reported diabetes, and HbA1c. RESEARCH DESIGN AND METHODS: Data from a population-based study of diet, cancer, and chronic disease were analyzed. A total of 2,898 men and 3,560 women 45-74 years of age who were registered with general practices in Norfolk, U.K., were recruited to the European Prospective Investigation Into Cancer-Norfolk study between 1995 and 1998. RESULTS: Mean plasma vitamin C levels were significantly higher in individuals with HbA1c levels < 7% than in those with self-reported diabetes or prevalent undiagnosed hyperglycemia (HbA1c > or = 7%). An inverse gradient of mean plasma vitamin C was found in both sexes across quintiles of HbA1c distribution < 7%. The odds ratio (95% CI) of having prevalent undiagnosed hyperglycemia per 20 micromol/l (or 1 SD) increase in plasma vitamin C was 0.70 (0.52-0.95) (adjusted for sex, age, BMI, waist-to-hip ratio, tertiary education, any use of dietary supplements, vegetarian diet, alcohol consumption, physical activity, dietary vitamin E, dietary fiber, dietary saturated fat, and smoking history). The unadjusted change in HbA1c per 20 micromol/l increase in vitamin C estimated by linear regression was -0.12% (-0.14 to -0.09) in men and -0.09% (-0.11 to -0.07) in women. After adjusting for the possible confounders, these values were -0.08% (-0.11 to -0.04) in men and -0.05% (-0.07 to -0.03) in women. CONCLUSIONS: An inverse association was found between plasma vitamin C and HbA1c. Dietary measures to increase plasma vitamin C may be an important public health strategy for reducing the prevalence of diabetes.

Postprandial hyperinsulinaemia, insulin resistance and inappropriately high phosphaturia are features of younger males with idiopathic calcium urolithiasis: attenuation by ascorbic acid supplementation of a test meal.

Schwille PO, Schmiedl A, Herrmann U, Wipplinger J. Department of Surgery, University of Erlangen, Germany.

Urol Res 1997;25(1):49-58

In idiopathic recurrent calcium urolithiasis (RCU) the state of insulin and carbohydrate metabolism, and relationships to minerals such as phosphate, are insufficiently understood. Therefore, in two groups of males with RCU (n = 30) and healthy controls (n = 8) the response to an oral carbohydrate- and calcium-

rich test meal was studied with respect to glucose, insulin, and C-peptide in peripheral venous blood (taken before and up to 180 min post-load), and phosphate and glucose in fasting and post-load urine. In one RCU group (n = 16) the meal was supplemented with ascorbic acid (ASC; 5 mg/kg body weight). The mean age (RCU 29, RCU + ASC 30, controls 27 years) and mean body mass index [RCU 24.4, RCU + ASC 25.0, controls 24.0 kg/m2] were similar. Insulin resistance (synonymous sensitivity of peripheral organs to insulin) was calculated from insulin serum concentration, as was also integrated insulin, C-peptide, and glucose. Untreated stone patients (RCU) developed hyperinsulinaemia between 60 and 120 min post-load, increased integrated insulin, and insulin resistance (P < or = 0.05 vs controls), whereas the rise of C-peptide and glycaemia (absolute and integrated values) was only of borderline significance. Fasting phosphaturia was low in both RCU subgroups vs controls; however, phosphaturia in untreated RCU rose in response to the meal, contrasting sharply with a decrease in controls. ASC supplementation of the meal (in the RCU + ASC subgroup) normalized insulin, failed to normalize post-load phosphaturia, but reduced post-load glucosuria and urinary pH significantly (mean pH values 5.55 vs 5.93 in untreated RCU, controls 5.50). Postprandial urinary oxalate, calcium, protein, and supersaturation products were not changed. The postprandial changes in phosphaturia and insulin sensitivity were inversely correlated (n = 38, r = -0.44, P = 0.007). It was concluded that in younger RCU males: (1) postprandial hyperinsulinaemia, the failure to reduce phosphaturia and - within limits - glucosuria, appropriately, as well as poor urine acidification are important features of the metabolism; (2) these phenomena are probably caused by insulin resistance of organs, the kidney included; and (3) the addition of a supraphysiological dose of ASC to a meal, the subsequent abolition of hyperinsulinaemia, and the restoration of normal urine acidification suggest that this antioxidant is capable of counteracting some pre-existing basic abnormality of cell metabolism in RCU.

Low plasma ascorbate levels in patients with type 2 diabetes mellitus consuming adequate dietary vitamin C.

Sinclair AJ, Taylor PB, Lunec J, Girling AJ, Barnett AH. University Department of Geriatric Medicine, Cardiff Royal Infirmary, UK.

Diabet Med 1994 Nov;11(9):893-8

Low ascorbate concentrations in diabetes may be secondary to inadequate dietary vitamin C intake or may relate to the varied metabolic roles of the vitamin. To determine whether inadequate dietary intake is a factor we calculated daily vitamin C intakes using both a vitamin C questionnaire and a 4-day food diary in a group of 30 patients with Type 2 diabetes (mean age 68.8 +/- 6.9 yr, 17M/13F) and in 30 community controls (mean age 68.0 +/- 5.5 yr, 12M/18F)). Measures of plasma glucose, serum fructosamine, and plasma ascorbic and dehydroascorbic acid were obtained from 20 subjects in each group. There was no significant difference in daily vitamin C intake between the two groups using both methods: food diary, 61.4 +/- 28.3 (patients) vs 69.5 +/- 33.4 (controls) mg; questionnaire, 54.0 +/- 28.9 (patients) vs 65.0 +/- 30.9 (controls) mg. Vitamin C intake derived

from both methods was significantly correlated (p < 0.001). Plasma ascorbate (30.4 +/- 19.1 mumol l-1) and dehydroascorbate (27.6 +/- 6.4 mumol l-1) levels were significantly lower in patients vs in controls (68.8 +/- 36.0 and 31.8 +/- 4.8 mumol l-1, respectively), p < 0.0001 and p < 0.01. Plasma ascorbate levels were significantly correlated with vitamin C intake derived from the food diary (p < 0.01) and questionnaire (p < 0.01) methods in the diabetic group only. Low ascorbate levels in diabetes appears to be a consequence of the disease itself and not due to inadequate dietary intake of vitamin C. A short vitamin C questionnaire is a convenient and reliable estimate of vitamin C intake.(ABSTRACT TRUNCATED AT 250 WORDS)

Plasma insulin responses after ingestion of different amino acid or protein mixtures with carbohydrate.

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Am J Clin Nutr 2000 Jul;72(1):96-105

BACKGROUND: Protein induces an increase in insulin concentrations when ingested in combination with carbohydrate. Increases in plasma insulin concentrations have been observed after the infusion of free amino acids. However, the insulinotropic properties of different amino acids or protein (hydrolysates) when co-ingested with carbohydrate have not been investigated.

OBJECTIVE: The aim of this study was to define an amino acid and protein (hydrolysate) mixture with a maximal insulinotropic effect when co-ingested with carbohydrate.

DESIGN: Eight healthy, nonobese male subjects visited our laboratory, after an overnight fast, on 10 occasions on which different beverage compositions were tested for 2 h. During those trials the subjects ingested 0.8 g*kg(-)(1)*h(-)(1) carbohydrate and 0.4 g*kg(-)(1)*h(-)(1) of an amino acid and protein (hydrolysate) mixture.

RESULTS: A strong initial increase in plasma glucose and insulin concentrations was observed in all trials, after which large differences in insulin response between drinks became apparent. After we expressed the insulin response as area under the curve during the second hour, ingestion of the drinks containing free leucine, phenylalanine, and arginine and the drinks with free leucine, phenylalanine, and wheat protein hydrolysate were followed by the largest insulin response (101% and 103% greater, respectively, than with the carbohydrate-only drink; P < 0.05).

CONCLUSIONS: Insulin responses are positively correlated with plasma leucine, phenylalanine, and tyrosine concentrations. A mixture of wheat protein

hydrolysate, free leucine, phenylalanine, and carbohydrate can be applied as a nutritional supplement to strongly elevate insulin concentrations.

Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients.

Velussi M, Cernigoi AM, De Monte A, Dapas F, Caffau C, Zilli M. Anti-Diabetes Centre, Monfalcone Hospital, Gorizia, Italy.

J Hepatol 1997 Apr;26(4):871-9

BACKGROUND/AIMS: Several studies have demonstrated that diabetic patients with cirrhosis require insulin treatment because of insulin resistance. As chronic alcoholic liver damage is partly due to the lipoperoxidation of hepatic cell membranes, anti-oxidizing agents may be useful in treating or preventing damage due to free radicals. The aim of this study was to ascertain whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis.

METHODS: A 12-month open, controlled study was conducted in two well-matched groups of insulin-treated diabetics with alcoholic cirrhosis. One group (n=30) received 600 mg silymarin per day plus standard therapy, while the control group (n=30) received standard therapy alone. The efficacy parameters, measured regularly during the study, included fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria levels, glycosylated hemoglobin (HbA1c) and malondialdehyde levels.

RESULTS: There was a significant decrease (p<0.01) in fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria and HbA1c levels already after 4 months of treatment in the silymarin group. In addition, there was a significant decrease (p<0.01) in fasting insulin levels and mean exogenous insulin requirements in the treated group, while the untreated group showed a significant increase (p<0.05) in fasting insulin levels and a stabilized insulin need. These findings are consistent with the significant decrease (p<0.01) in basal and glucagon-stimulated C-peptide levels in the treated group and the significant increase in both parameters in the control group. Another interesting finding was the significant decrease (p<0.01) in malondialdehyde/levels observed in the treated group.

CONCLUSIONS: These results show that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.

Inhibition of aldose reductase in human erythrocytes by vitamin C.

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Diabetes Res Clin Pract 1999 Jan;43(1):1-8

Ascorbic acid, or vitamin C, has been reported to lower erythrocyte sorbitol concentrations, and present studies were performed to determine the mechanism of this effect. Incubation of erythrocytes with increasing concentrations of glucose (5-40 mM) progressively increased erythrocyte sorbitol contents, reflecting increased flux through aldose reductase. At extracellular concentrations of 90 microM, both ascorbic acid and its oxidized form, dehydroascorbate, decreased intracellular sorbitol by 25 and 45%, respectively. This inhibition was not dependent on the extracellular glucose concentration, or on erythrocyte contents of free NADPH or GSH. To test for a direct effect of ascorbate on aldose reductase, erythrocyte hemolysates were prepared and supplemented with 100 microM NADPH. Hemolysates reduced glucose to sorbitol in a dose-dependent manner that was inhibited with a Ki of 120 microM by the aldose reductase inhibitor tetramethylene glutaric acid. Above 100 microM, ascorbic acid also lowered hemolysate sorbitol generation by about 30%. Studies with ascorbic acid derivatives showed that the reducing capacity of ascorbic acid was not required for inhibition of sorbitol production from glucose in erythrocyte hemolysates. These results show that high, but physiologic, concentrations of ascorbic acid can directly inhibit erythrocyte aldose reductase, and provide a rationale for the use of oral vitamin C supplements in diabetes.

Reduced serum dehydroepiandrosterone levels in diabetic patients with hyperinsulinaemia.

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Clin Endocrinol (Oxf) 1998 Sep;49(3):377-83

OBJECTIVE: To elucidate the interaction between insulin and dehydroepi-androsterone (DHEA) concentrations, we evaluated serum DHEA and DHEA-sulphate (DHEA-S) levels in diabetic patients with hyperinsulinaemia.

PATIENTS AND DESIGN: Twenty-four subjects with non-insulin dependent diabetes mellitus, 12 hyperinsulinaemic subjects (fasting serum insulin concentrations > or = 10 mU/ml (71.8 pmol/l)) and 12 non-hyperinsulinaemic subjects, and 10 normal control subjects were studied. Serum DHEA, DHEA-S, cortisol and ACTH levels were investigated in these subjects. Moreover, their serum DHEA levels were compared during hyperinsulinaemic-euglycaemic clamp and after ACTH stimulation.

MEASUREMENTS: Serum insulin, cortisol, ACTH, DHEA and DHEA-S concentrations were evaluated by RIA. Serum glucose was determined by the glucose oxidase method.

RESULTS: Diabetic patients with hyperinsulinaemia showed significantly lower levels of serum DHEA and DHEA-S than controls. After ACTH stimulation,

these patients also showed significantly lower DHEA levels. During the hyperinsulinaemic-euglycaemic clamp, serum DHEA concentrations of diabetic patients with hyperinsulinaemia remained low and did not decline further, although those of control subjects and non-hyperinsulinaemic diabetic patients showed a significant decline of serum DHEA levels. Even after ACTH stimulation during the clamp, serum DHEA in hyperinsulinaemic patients was still significantly lower than in controls.

CONCLUSIONS: In diabetic patients with hyperinsulinaemia, baseline DHEA levels are chronically and maximally suppressed compared to control subjects and non-hyperinsulinaemic diabetic patients, and thus not decreased further by exogenous insulin infusion during hyperinsulinaemic-euglycaemic clamp.

Biotin administration improves the impaired glucose tolerance of streptozotocin-induced diabetic Wistar rats.

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J Nutr Sci Vitaminol (Tokyo) 1997 Jun;43(3):271-80

The effect of biotin administration on the glucose tolerance of streptozotocin (STZ)-induced diabetic Wistar rats was investigated. STZ-induced diabetes was induced by intraperitoneal injection of streptozotocin (45 mg/kg body weight as a single dose). The impaired glucose tolerance in response to an oral glucose load (1.8g per kg body weight) in STZ-induced diabetic rats (STZ-rat) was partially improved by intraperitoneal administration of biotin for 15 days (100 micrograms/rat/day). However, a recovery in the STZ-rat's insulin secretion was not found after biotin administration. To help clarify the mechanism underlying the improvement in glucose tolerance seen with biotin treatment, glucokinase and hexokinase activities were determined in the liver and pancreas. In STZ-rats that had received biotin (STZ-biotin rats), glucokinase activity was higher by 3.4-fold in liver and by 2.4-fold in pancreas than in the STZ-rats. The biotin level of STZ-rats was significantly lower in the liver and pancreas than that of the control rats (no STZ administration); but in STZ-biotin rats, the level in these organs recovered to the control level. These results demonstrate that injected biotin can improve glucose handling without increasing insulin secretion in STZ-rats.

Improvement of oral glucose tolerance in gestational diabetes by pyridoxine.

Bennink HJ, Schreurs WH
Br Med J 1975 Jul 5;3(5974):13-5

Fourteen pregnant women were shown by the oral glucose tolerance test to have gestational diabetes. In 13 an increased urinary xanthurenic-acid excretion after an oral load of L-tryptophan indicated a relative pyridoxine deficiency. All patients were treated with vitamin B6 (pyridoxine) 100 mg/day for 14 days by mouth, after which the pyridoxine deficiency disappeared and the oral glucose tolerance improved considerably. Only two patients then had sufficiently impaired

glucose tolerance to justify the diagnosis of gestational diabetes; Our results substantiated our hypothesis that increased xanthurenic-acid synthesis during pregnancy may cause gestational diabetes. Treatment with vitamin B6 makes the production of xanthurenic-acid normal by restoring tryptophan metabolism and improves the oral glucose tolerance in patients with gestational diabetes.

Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, and noninsulin-dependent diabetes in postmenopausal women: the Rancho Bernardo Study.

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J Clin Endocrinol Metab 1996 Jan;81(1):59-64

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) levels were determined in morning specimens from 659 fasting postmenopausal women who were not using estrogen therapy or antidiabetic medication. All women had concurrent oral glucose tolerance tests and measurements of body mass index (BMI) and waist-hip ratio (WHR). DHEA levels were weakly and inversely associated with BMI but not with WHR or glucose tolerance status. DHEAS levels were not associated with BMI but were positively associated with WHR, diabetes, and impaired glucose tolerance. In analyses adjusted for or stratified by WHR, the DHEAS association with abnormal carbohydrate tolerance was reduced but still independent of fat distribution. Because this was a cross-sectional study, it was not possible to determine whether DHEAS levels were raised by central obesity or vice versa. At a minimum, these data strongly suggest that the positive association of DHEAS with both central obesity and abnormal glucose tolerance does not support the thesis that DHEAS protect against diabetes or obesity in older women as had been suggested by animal studies.

Differential expression of hepatic oestrogen, phenol and dehydroepiandrosterone sulphotransferases in genetically obese diabetic (ob/ob) male and female mice.

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Department of Biochemical Medicine, University of Dundee, Ninewells Hospital and Medical School, UK.
J Endocrinol 1995 Jan;144(1):31-7

Sulphotransferases (STs) are a family of closely related enzymes playing a key role in regulation of the bioavailability and activity of important endogenous molecules such as steroid hormones. A relationship between the expression of steroid STs and the diabetic state has been demonstrated in various laboratory animal models, and steroid sulphates such as dehydroepiandrosterone sulphate are

known to have anti-diabetic properties. In order to further our understanding of the molecular basis for the association of steroid hormone sulphation and diabetes, we have examined the expression of oestrogen, phenol and dehydroepiandrosterone (DHEA) STs in mice carrying the obesity mutation (ob), which in the homozygous state (ob/ob) produces mice which are obese and diabetic. Our data show that, in male mice, ST activities towards oestrone (E1), oestriol (E3), DHEA and the xenobiotic 1-naphthol are elevated in ob/ob mice, whereas in female mice, only the oestrogen ST activities were elevated, with the DHEA and 1-naphthol ST activities reduced. Using antibodies directed against oestrogen ST, it was demonstrated that the induction of E1 and E3 ST activity in ob/ob mice correlated with the expression of an ST isoenzyme not constitutively expressed in control mouse liver.

Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men.

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Department of Medicine, University of Texas Health Science Center, San Antonio, TX 78284
Metabolism 1994 May;43(5):599-603

Although many studies indicate that increased androgenicity is associated with insulin resistance and hyperinsulinemia in both premenopausal and postmenopausal women, relatively few data are available on this relationship in men. We examined the association of sex hormone-binding globulin (SHBG), total and free testosterone, dehydroepiandrosterone sulfate (DHEA-SO4), and estradiol to glucose and insulin concentrations before and during an oral glucose tolerance test in 178 men from the San Antonio Heart Study, a population-based study of diabetes and cardiovascular disease. Total and free testosterone and DHEA-SO4 were significantly inversely associated with insulin concentrations. Free testosterone and DHEA-SO4 were also significantly inversely correlated with glucose concentrations. SHBG was weakly positively associated with glucose concentrations. Estradiol was not related to glucose or insulin concentrations. After adjustment for age, obesity, and body fat distribution, insulin concentrations remained significantly inversely correlated with free testosterone ($r = -.23$), total testosterone ($r = -.21$), and DHEA-SO4 ($r = -.21$; all $P < .01$). In conclusion, we observed that increased testosterone and DHEA-SO4 are associated with lower insulin concentrations in men. This is in striking contrast to women, where increased androgenicity is associated with insulin resistance and hyperinsulinemia.

[Dehydroepiandrosterone. Renaissance after 13 years]

Sonka J
Cas Lek Cesk 1989 Sep 8;128(37):1157-60

DHEA, a steroid precursor of androgens and estrogens has also an inhibitory effect on several enzymes, namely on 11 beta-hydroxylase, NADH oxidase and glucose 6-phosphate dehydrogenase. The latter is the rate limiting enzyme of the pentose phosphate cycle. This metabolic pathway provides the cells with extramitochondrial NADPH and pentose phosphates. NADPH is used for the synthesis of fatty acids and steroids. Together with ribose 5-phosphate, NADPH (as coenzyme of folate reductases) is required for the synthesis of nucleic acids. A deficient production of DHEA has been found to be responsible for several diseases obesity, diabetes type 2, hypertension, arteriosclerosis and hyperuricemia as well as malignant growth (low DHEA syndrome). DHEA administration favourably modified several of these metabolic disorders. These studies were started in our laboratory in 1962 and stopped in 1976 because we were short of DHEA. At that time the response to our results was rather theoretical, but the last years a new wave of interest in DHEA called for two consecutive symposia, where important findings were presented (Paris in January and Jena in April 1989). It is a damage that this new trend, started in our laboratory, could not be pursued up to now without interruption.

[Effect of androgen on the onset of diabetes in the KK mice treated with monosodium aspartate]

Higuchi N, Sasaki M, Arai T, Oki Y
Department of Veterinary Biochemistry, Nippon Veterinary and Zootechnical College, Tokyo, Japan.
Jikken Dobutsu 1989 Jan;38(1):25-9

Obese diabetes was induced by monosodium aspartate (MSA) administration in KK male mice and the diabetic KK mice were divided into two groups, younger (12-week-old) and older (35-week-old). The diabetic KK mice were castrated and administered with androgen and effect of androgen on glycosuria appearance was investigated. Androgen dependent tear proteins (Mtp-M) were detected by the method of polyacrylamide gel electrophoresis. Blood androgen level was estimated by observation of change of the pattern of Mtp-M. In the younger mice group, glycosuria disappeared temporarily after castration and then appeared naturally again. The Mtp-M declined with castration, but did not disappear in this experimental period. In the older mice group, glycosuria and Mtp-M disappeared completely and blood glucose level decreased considerably after castration. However, in the castrated older mice, the glycosuria and the Mtp-M appeared again after the administration of dehydroepiandrosterone (DHEA), and the increasing of blood glucose level was observed. These results strongly suggested that androgen had an important role in the onset of diabetes in the KK mice treated with MSA.

Therapeutic effects of dehydroepiandrosterone (DHEA) and its metabolites in obese-hyperglycemic mutant mice.

Coleman DL
Jackson Laboratory, Bar Harbor, ME 04609.
Prog Clin Biol Res 1988;265:161-75

Dehydroepiandrosterone (DHEA) fed at 0.4%, and its metabolites, 3 alpha-hydroxyetiocholanolone (alpha-ET) and 3 beta-hydroxyetiocholanolone (beta-ET), fed at 0.1%, had marked anti-hyperglycemic and anti-obesity properties in mutant mice with single gene obesity mutations (diabetes, db; obese, ob; viable yellow, Avy). The therapeutic effects differed depending on the mutation as well as the inbred background on which the mutation was maintained. These steroids prevented onset of hyperglycemia and reduced the rate of weight gain in C57BL/6J-db/db and ob/ob mice, whereas in C57BL/KsJ-db/db mice, only hyperglycemia was prevented. The viable yellow (Avy) mutant, exhibiting a more slowly developing obesity condition, responded to all steroids with a marked decrease in rate of weight gain associated with decreased plasma insulin concentrations. Steroid treatment of most mouse mutants was associated with normal or increased food intake, a feature that suggests a decrease in metabolic efficiency. In order to assess any potential energy wastage by steroid stimulation of futile cycles we looked at the rates of lipogenesis, gluconeogenesis and oxygen consumption in steroid-treated normal and mutant mice. With the possible exception of the rate of gluconeogenesis that in obesity mutants was consistently reduced to normal by treatment, no metabolic changes were of sufficient magnitude to account for the marked decrease in metabolic efficiency. All treatments potentiated the action of insulin. This potentiation may change the hormonal balance such that minor changes in the rates of many metabolic pathways may interact to produce a large decrease in metabolic efficiency.

Modulation of growth, differentiation and carcinogenesis by dehydroepiandrosterone.

Gordon GB, Shantz LM, Talalay P
Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
Adv Enzyme Regul 1987;26:355-82

Dehydroepiandrosterone (3 beta-hydroxy-5-androsten-17-one; DHEA) and its conjugates are abundant circulating steroids that originate largely from the adrenal cortex. Their levels decline profoundly with age in human beings of both sexes, as the incidence of most cancers rises. Low levels of these steroids have been associated with the presence and risk ofdevelopment of cancer. Administration of DHEA to rodents produces protection against spontaneous tumors and chemical carcinogenesis, suppresses weight gain without significantly affecting food intake,

ameliorates the severity of diabetes in genetically diabetic mice, and restrains autoimmune processes. DHEA and related steroids also depress the mitogenic effects of carcinogens, tumor promoters and plant lectins, and block viral and carcinogen-induced cell transformations. DHEA and certain congeners are also potent and quite specific inhibitors of mammalianglucose-6-phosphate dehydrogenases. We have observed that the conversion of 3T3-L1 and 3T3-F442A preadipocyte clones to the adipocyte phenotype, in response to appropriate differentiation stimuli (fetal calf serum, insulin, dexamethasone, and 1-methyl-3-isobutylxanthine), is blocked by DHEA and other steroidal inhibitors of glucose-6-phosphate dehydrogenase. The structural requirements for blocking adipocyte differentiation and for inhibiting glucose-6-phosphate dehydrogenase are closely correlated. Evidence is reviewed suggesting that the inhibition of glucose-6-phosphatedehydrogenase is central to the anticarcinogenic and differentiation-blocking actions of DHEA and related steroids. The 3T3 preadipocyte clones provide a valuable system for the analysis of the mechanisms of the effects of DHEA on growth, differentiation and carcinogenesis. (94 Refs.)

Androgenic and estrogenic metabolites in serum of mice fed dehydroepiandrosterone: relationship to antihyperglycemic effects.

Leiter EH, Beamer WG, Coleman DL, Longcope C
Metabolism 1987 Sep;36(9):863-9

The steroid prehormone, dehydroepiandrosterone (DHEA) has potentanti hyperglycemic effects when fed in the diet of genetically diabetic C57BL/KsJ-db/db mice. The purpose of this investigation was to analyze changes in sex steroid levels in serum of mice fed DHEA, and to compare the antihyperglycemic potencies of the various metabolites in order to clarify the mechanism of DHEA action. Steroid radioimmunoassays showed that dietary DHEA entered the blood in high concentrations and was actively metabolized to both androgens (testosterone, T; dihydrotestosterone, DHT) and estrogens (estrone, E1; 17 beta-estradiol, E2). This metabolism did not require intact adrenal glands or gonads. In C57BL/KsJ normal (+/+) males, conversion of DHEA to androgens was the prominent feature; in db/db males, DHEA feeding not only increased serum T and DHT, but also serum E1 and E2 levels. The db/db mice had increased amounts of adipose tissue that sequestered more intravenously injected 3H-E2; this additional body fat could account for increased aromatization of DHEA-derived estrogen precursors. Comparisons of the relative antihyperglycemic potencies of androgenic and estrogenic steroid metabolites of DHEA in db/db mice showed that the estrogens and metabolites with estrogenic properties (androstenediol) or those convertible to estrogens (DHEA sulfate) were the most potent. Although 17 beta-E2 was effective by injection or per os, DHEA was effective only when administered per os, implicating alimentary tract conversion of DHEA to more biologically active reactants. Based on the pivotal position of DHEA as a prehormone for androgens, estrogens, andetiocholanolones, an explanation of the seemingly paradoxical effects exerted by this compound in blocking autoimmune disease, hyperglycemia, obesity, and neoplasia was proposed

Effect of genetic background on the therapeutic effects of dehydroepiandrosterone (DHEA) in diabetes-obesity mutants and in aged normal mice.

Coleman DL, Schwizer RW, Leiter EH
Diabetes 1984 Jan;33(1):26-32

Dehydroepiandrosterone (DHEA) was fed at 0.1-0.4% in the diet to genetically diabetic (db/db) or obese (ob/ob) C57BL/KsJ (BL/Ks) or C57BL/6J (BL/6) mice. Treatment of BL/Ks-db/db or ob/ob mice with 0.4% DHEA prevented hyperglycemia, islet atrophy, and severe diabetes associated with this inbred background, but did not affect weight gain and food consumption. Homozygous obese (ob) or diabetes (db) mice on the BL/6 background were more sensitive to DHEA, and the mild, transient hyperglycemia associated with ob or db gene expression on the BL/6 inbred background could be prevented by 0.1% DHEA. Both body weight and food consumption were decreased in BL/6 mutants maintained on 0.1% DHEA whereas this effect was not seen in BL/Ks mutants fed up to 0.4% DHEA. Early therapy with 0.4% DHEA, initiated at 2 wk of age, prevented the developmentof most diabetes symptoms and decreased the rate of weight gain in pups of all genotypes. In addition to therapeutic effects on both obese mutants, DHEA effected significant changes in an aging study using normal BL/6 female mice. Four weeks of DHEA treatment initiated at 2 yr of age improved glucose tolerance and at the same time reduced plasma insulin to a "younger" level. This suggests that DHEA may act in insulin-resistant mutant mice and in aging normal mice to increase the sensitivity to insulin.

Therapeutic effects of dehydroepiandrosterone (DHEA) in diabetic mice.

Coleman DL, Leiter EH, Schwizer RW
Diabetes 1982 Sep;31(9):830-3

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 aglucose 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 insulitis, 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.

Interaction of alpha-lipoic acid enantiomers and homologues with the enzyme components of the mammalian pyruvate dehydrogenase complex.

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Biochem Pharmacol 1995 Aug 25;50(5):637-46

Lipoic acid (alpha-lipoic acid, thioctic acid) is applied as a therapeutic agent in various diseases accompanied by polyneuropathia such as diabetes mellitus. The stereoselectivity and specificity of lipoic acid for the pyruvate dehydrogenase complex and its component enzymes from different sources has been studied. The dihydrolipoamide dehydrogenase component from pig heart has a clear preference for R-lipoic acid, a substrate which reacts 24 times faster than the S-enantiomer. Selectivity is more at the stage of the catalytic reaction than of binding. The Michaelis constants of both enantiomers are comparable (Km = 3.7 and 5.5 mMfor R- and S-lipoic acid, respectively) and the S-enantiomer inhibits the R-lipoic acid dependent reaction with an inhibition constant similar to its Michaelis constant. When three lipoic acid homologues were tested, RS-1,2-dithiolane-3-caproic acid was one carbon atom longer than lipoic acid, while RS-bisnorlipoic acid and RS-tetranorlipoic acid were two and four carbon atoms shorter, respectively. All are poor substrates but bind to and inhibit the enzyme with an affinity similar to that of S-lipoic acid. No essential differences with respect to its reaction with lipoicacid enantiomers and homologues exist between free and complex-bound dihydrolipoamide dehydrogenase. Dihydrolipoamide dehydrogenase from human renal carcinoma has a higher Michaelis constant for R-lipoic acid (Km = 18mM) and does not accept the S-enantiomer as a substrate. Both enantiomers of lipoic acid are inhibitors of the overall reaction of the bovine pyruvate dehydrogenase complex, but stimulate the respective enzyme complexes from rat as well as from Escherichia coli. The S-enantiomer is the stronger inhibitor, the R-enantiomer the better activator. The two enantiomers have no influence on the partial reaction of the bovine pyruvate dehydrogenase component, but do inhibit this enzyme component from rat kidney. The implications of these results are discussed.

alpha-Lipoic acid as a biological antioxidant.

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Free Radic Biol Med 1995 Aug;19(2):227-50

alpha-Lipoic acid, which plays an essential role in mitochondrial dehydrogenase reactions, has recently gained considerable attention as an antioxidant. Lipoate, or its reduced form, dihydrolipoate, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may in turn recycle vitamin E. In addition to its antioxidant activities, dihydrolipoate may exert prooxidant actions through reduction of iron. alpha-Lipoic acid administration has been shown to be beneficial in a number of oxidative stress models such as ischemia-reperfusion injury, diabetes (both alpha-lipoic acid and dihydrolipoic acid exhibit hydrophobic binding to proteins such as albumin, which can prevent glycation reactions), cataract formation, HIV activation, neurodegeneration, and radiation injury. Furthermore, lipoate can function as a redox regulator of proteins such as myoglobin, prolactin, thioredoxin and NF-kappa B transcription factor. We review the properties of lipoate in terms of

(1) reactions with reactive oxygen species;
(2) interactions with other antioxidants;
(3) beneficial effects in oxidative stress models or clinical conditions. (153 Refs.)

[Diabetes mellitus--a free radical-associated disease. Results of adjuvant antioxidant supplementation]

Kahler W, Kuklinski B, Ruhlmann C, Plotz C
Klinik fur Innere Medizin, Klinikums Rostock-Sudstadt.
Z Gesamte Inn Med 1993 May;48(5):223-32

Our investigations carried out in patients with diabetes mellitus revealed oxidative stress loads. The study presented here was to clarify whether a therapy with antioxidants can contribute to an improvement of prognosis. 80 patients affected with a long term diabetic late syndrome were randomised and arranged to 4 groups of n = 20 each. In contrast to a control group these patients received 600 mg of alpha lipoic acid or 100 micrograms of selenium (sodium selenite) daily or 1200 IE of D-alpha-tocopherol respectively for a time of 3 months. In comparison with the control group all groups treated in an antioxidative way showed significantly diminished serum concentrations of thiobarbituric acid reactive substances and of urinary albumin excretion rates. The symptoms of distal symmetric neuropathy measured according to the thermo- and vibration sensitivity also improved in a highly significant manner. The results prove that oxidative stress plays a promoting role in developing of long term diabetic late complications and that a therapy with adjuvant antioxidants may lead to a regression of diabetic late complications.

Lipoate prevents glucose-induced protein modifications.

Suzuki YJ, Tsuchiya M, Packer L
Department of Molecular & Cell Biology, University of California, Berkeley 94720.
Free Radic Res Commun 1992;17(3):211-7

Nonenzymatic glycation has been found to increase in a variety of proteins in diabetic patients. The present study examined a possibility of preventing glycation and subsequent structural modifications of proteins by alpha-lipoic acid (thioctic acid) as lipoate, a substance which has gained attention as a potential therapeutic agent for diabetes-induced complications. Incubation of bovine serum albumin (BSA) at 2 mg/ml with glucose (500 mM) in a sterile condition at 37 degrees C for seven days caused glycation and structural modifications of BSA observed by SDS-PAGE, near UV absorption, tryptophan and nontryptophan fluorescence, and fluorescence of an extrinsic probe, TNS (6-(p-toluidinyl) naphthalene-2-sulfonate). When BSA and glucose were incubated in the presence of lipoate (20mM), glycation and structural modifications of BSA were significantly prevented. Glycation and inactivation of lysozyme were also prevented by lipoate. These results suggest a potential for the therapeutic use of lipoic acid against diabetes-induced complications.

Neural dysfunction and metabolic imbalances in diabetic rats. Prevention by acetyl-L-carnitine.

Ido Y, McHowat J, Chang KC, Arrigoni-Martelli E, Orfalian Z, Kilo C, Corr PB, Williamson JR
Department of Pathology, Washington University School of Medicine, St. Louis, Missouri 63110.
Diabetes 1994 Dec;43(12):1469-77

The rationale for these experiments is that administration of L-carnitine and/or short-chain acylcarnitines attenuates myocardial dysfunction

1) in hearts from diabetic animals (in which L-carnitine levels are decreased);
2) induced by ischemia-reperfusion in hearts from nondiabetic animals; and
3) in nondiabetic humans with ischemic heart disease.

The objective of these studies was to investigate whether imbalances in carnitine metabolism play a role in the pathogenesis of diabetic peripheral neuropathy. The major findings in rats with streptozotocin-induced diabetes of 4-6 weeks duration were that 24-h urinary carnitine excretion was increased approximately twofold and L-carnitine levels were decreased in plasma (46%) and sciatic nerve endoneurium (31%). These changes in carnitine levels/excretion were associated with decreased caudal nerve conduction velocity (10-15%) and sciatic nerve changes in Na(+)-K(+)-ATPase activity (decreased 50%), Mg(2+)-ATPase (decreased 65%), 1,2-diacyl-sn-glycerol (DAG) (decreased 40%), vascular

albumin permeation (increased 60%), and blood flow (increased 65%). Treatment with acetyl-L-carnitine normalized plasma and endoneurial L-carnitine levels and prevented all of these metabolic and functional changes except the increased blood flow, which was unaffected, and the reduction in DAG, which decreased another 40%. In conclusion, these observations

1) demonstrate a link between imbalances in carnitine metabolism and several metabolic and functional abnormalities associated with diabetic polyneuropathy and
2) indicate that decreased sciatic nerve endoneurial ATPase activity (ouabain-sensitive and insensitive) in this model of diabetes is associated with decreased DAG.

Serum and urine levels of levocarnitine family components in genetically diabetic rats.

Morabito E, Corsico N, Marzo A, Arrigoni Martelli E
Department of Pharmacology, Sigma-Tau S.p.A., Pomezia, Roma, Italy.
Arzneimittelforschung 1994 Aug;44(8):965-8

Serum concentration and urinary excretion of levocarnitine (L-carnitine, CAS 541-15-1) family components were evaluated in a Wistar derived strain of genetically diabetic rats BB/BB, in comparison with normal Wistar rats, and their control rats BB/WB of both sexes. BB/BB diabetic animals have lower serum concentration of total-L-carnitine (TC), L-carnitine (LC), acetyl-L-carnitine (ALC), and short chain L-carnitine esters (SCLCE) than both the strains of non-diabetic rats, as previously observed in streptozotocin diabetic rats. No or marginal variations between control and diabetic rats were detected in cumulative urinary excretion of L-carnitine family components. A strain difference was observed between Wistar and BB/WB non-diabetic rats, BB/WB showing higher serum concentration and lower cumulative urinary excretion of LC and TC than Wistar animals. Renal clearance of L-carnitine components proved to be markedly higher in BB/BB diabetic rats, as previously shown in streptozotocin rats. The reduction of serum concentration of the carnitines endogenous pool may explain this finding. The lack of an increased urinary excretion of L-carnitine components in diabetic animals despite the high increase of diuresis suggests that the saturable tubular reabsorption of L-carnitine family components also in diabetes is the primary mechanism to preserve the homeostatic equilibria of the L-carnitine family, the variation in serum concentration being attributable to the complex systemic metabolicalterations typical of diabetes. In agreement with previous investigations,male animals of all the strains showed higher serum concentration andurinary excretion of L-carnitine components as compared to females.

Acetyl-L-carnitine corrects electroretinographic deficits in experimental diabetes.

Lowitt S, Malone JI, Salem A, Kozak WM, Orfalian Z
Department of Pediatrics, University of South Florida, Tampa.
Diabetes 1993 Aug;42(8):1115-8

Acetyl-L-carnitine reduces the latencies of electroretinogram oscillatory potentials in healthy humans. The effect of acetyl-L-carnitine (50mg.kg-1.day-1) on the increased electroretinogram latencies found in rats with STZ-induced hyperglycemia of 3-wk duration was evaluated. The aldosereductase inhibitor sorbinil, which has been shown to normalize abnormal electroretinogram tracings associated with STZ-induced diabetes, was used as a positive control. Aldose reductase inhibitors are thought to lower tissue sorbitol while increasing myo-inositol. The electroretinograms of the STZ-induced diabetic rats in this study were abnormal; treatment withacetyl-L-carnitine as well as sorbinil significantly improved electroretinogram b-wave amplitude and decreased the latencies of oscillatory potentials 2 and 3. Acetyl-L-carnitine treatment of STZ-induced diabetic rats did not affect hyperglycemia or erythrocyte polyol pathway activity as reflected by erythrocyte sorbitol levels. In contrast, sorbinil did reduce elevated erythrocyte sorbitol levels. This suggests that the impaired electroretinograms associated with STZ-induced diabetes may not be caused solely by increased polyol pathway activity.

Acetyl-L-carnitine effect on nerve conduction velocity in streptozotocin-diabetic rats.

Morabito E, Serafini S, Corsico N, Martelli EA
Department of Pharmacology, Sigma-Tau S.p.A. Pomezia, Rome, Italy.
Arzneimittelforschung 1993 Mar;43(3):343-6

Measurement of nerve conduction velocity (NCV) is a useful and sensitive tool for evaluating diabetes related neurological dysfunctions. The method used allows to monitor the parameter at different times in the same group of rats, so that it is possible to observe simultaneously the development of the damage in time, and to evaluate the improvement related to the treatment. The repeated oral treatment with acetyl-L-carnitine (ALC, CAS 5080-50-2) 250 mg/kg caused an improvement in NCV of the diabetic rats; the effect was higher when the treatment started early with respect to the diabetes induction. The improvement in NCV was constant in time and comparable from 2 to 6 weeks of the treatment. In conclusion, oral treatment with ALC was able to normalize the impairment of NCV in streptozotocin rats, the effect being constant in time from 2 to 6 weeks of treatment and up to 8 weeks after induction when administration started in early stage of diabetes (2-3 weeks after induction); however, at this time the NCV is already significantly decreased.

Effect of acetyl-L-carnitine treatment on the levels of levocarnitine and its derivatives in streptozotocin-diabetic rats.

Marzo A, Corsico N, Cardace G, Morabito E
Department of Drug Metabolism and Pharmacokinetics, Sigma-Tau S.p.A., Pomezia, Rome, Italy.
Arzneimittelforschung 1993 Mar;43(3):339-42

The effect of diabetes induced by streptozotocin and that of acetyl-L-carnitine (ALC) hydrochloride (CAS 5080-50-2) treatment on the homeostasis of the levocarnitine (L-carnitine) moiety was investigated in Sprague-Dawley rats. The diabetic status was ascertained by measuring blood glucose. L-carnitine (LC), total acid soluble L-carnitine (TC) and ALC were measured in serum, tissues and urine by radioenzymatic methods. Short-chain L-carnitine esters (SCLCE) were obtained by subtracting LC from TC. Serum concentration of L-carnitine moiety was decreased in diabetic when compared to normal rats; whereas ALC oral treatment (50 and 150 mg/kg p.o. for 4 weeks) in diabetic rats increased, dose-dependently, all the components of L-carnitine moiety, SCLCE and ALC being completely restored. In the liverof diabetic rats all the analytes proved to be higher than in normal rats, mainly LC and TC. A similar trend was observed in skeletal muscle, at least with LC and TC, whereas SCLCE and ALC were not affected. The treatment with ALC increased the liver concentration of all the analytes in a dose-related way whereas in skeletal muscle only LC and TC showed an increase with the highest dose of ALC. Myocardium and kidneys showed a decrease of all the analytes in diabetes; the treatment with ALC normalized the situation in kidneys, in a dose-related way, but not in the myocardium. Urinary excretion and renal clearance of L-carnitine moiety increased in diabetes; an additional dose-related increase was observed with the ALC treatment.

Acetyl-L-carnitine prevents substance P loss in the sciatic nerve and lumbar spinal cord of diabetic animals.

Di Giulio AM, Gorio A, Bertelli A, Mantegazza P, Ferraris L, Ramacci MT
Department of Medical Pharmacology, University of Milan, Italy.
Int J Clin Pharmacol Res 1992;12(5-6):243-6

Diabetic neuropathy is a disease of peripheral nerves, characterized by axonal atrophy and degeneration that might be preceded by a marked impairment of axonal transport and by a reduced conduction velocity. Sensory nerves are particularly susceptible to diabetes. In the present report it is shown that experimental diabetes in rats causes a significant reduction of the content of the pain-related neuropeptide substance P insciatic nerve and lumbar spinal cord. Such a loss of substance P is fully prevented by acetyl-L-carnitine treatment. The neuroprotective pharmacological effect is selective and takes place without

significant changes of hyperglycaemia and without modifications of the reduced rate of body growth typical of diabetic animals.

Altered neuroexcitability in experimental diabetic neuropathy: effect of acetyl-L-carnitine.

Malone JI, Lowitt S, Corsico N, Orfalian Z
University of South Florida, Tampa.
Int J Clin Pharmacol Res 1992;12(5-6):237-41

Sciatic nerve conduction velocity (NCV) is reduced in rats made hyperglycaemic with streptozotocin (STZ). This neurophysiologicaldys function has been associated with increased nerve sorbitol and reduced nerve inositol. Treatment of STZ diabetic rats with aldose reductase inhibitors (ARIs) which reduce sorbitol and increase inositol in the nerve results in normalization of NCVs. Male Wistar rats were made diabetic with 50 mg/kg of streptozotocin given intraperitoneally. Those animals with blood glucose > 300 mg/dl two weeks later were included in this study. The STZ-diabetic rats were treated with either the ARI sorbinil (40 mg/kg per day), or acetyl-L-carnitine (ALC) (300 mg/kg per day) or sterile 0.15% aqueous NaCl for 16 weeks after 4 or 8 weeks of untreated hyperglycaemia. A control group of non-diabetic rats received no treatment during the interval. Sciatic-nerve sorbitol was elevated (1.08 +/- 0.13 nanomol/mg wet weight vs. 0.19 +/- 0.03 nm/mg wet weight) and inositol was reduced (1.21+/- 0.12 nm/mg ww vs. 2.02 +/- 0.08 nm/mg ww) in the STZ diabetic rats, which were untreated for 4 weeks. Treatment with sorbinil was associated with normalization of the tissue sorbitol (0.10 +/- 0.05 nm/mg ww), while ALC treatment also significantly reduced the nerve sorbitol but only to a level (0.34 +/- 0.08 nm/mg ww) more elevated than the normal level. The nerves of STZ animals treated with sorbinil or ALC had inositol levels no different from untreated diabetic rats. Thus, hyperglycaemic animals treated with either ALC or sorbinil had similar improvements in NCVs as the diabetic, even though the effect on nerve sorbitol was different and nerve inositol was unchanged.(ABSTRACT TRUNCATED AT 250 WORDS)

[The action of carnitine-series preparations in experimental alloxan diabetes mellitus]

Kim EK, Trevisani C, Trevisani M
Eksp Klin Farmakol 1992 Jul-Aug;55(4):35-6

The study was undertaken to examine the effects of l-carnitine and acetyl-l-carnitine in rats and mice with experimental alloxan diabetes. The findings suggest that acetyl-l-carnitine is more effective against diabetes in increasing glucose tolerance, restoring the impaired response of glucagon to glucose, showing glycogen-sparing action than is l-carnitine.

Effect of aminoguanidine on the frequency of neuroaxonal dystrophy in the superior mesenteric sympathetic autonomic ganglia of rats with streptozocin-induced diabetes.

Schmidt RE, Dorsey DA, Beaudet LN, Reiser KM, Williamson JR, Tilton RG
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Diabetes 1996 Mar;45(3):284-90

Aminoguanidine, which prevents formation of advanced glycation end products and is a relatively selective potent inhibitor of the inducible (versus constitutive) isoform(s) of nitric oxide synthase, has been reported to ameliorate structural and functional abnormalities in peripheral somatic nerves in rats with streptozocin (STZ)-induced diabetes. In the present studies, the effects of aminoguanidine treatment on ultrastructural changes in the autonomic nervous system of rats with STZ-induced diabetes were examined. The frequency of neuroaxonal dystrophy, the neuropathological hallmark of sympathetic autonomic neuropathy in diabetic rats, increased 9- to 11-fold in the superior mesenteric ganglia of 7- and 10-month STZ-diabetic rats compared with that in age-matched controls. Administration of aminoguanidine continuously from the time of induction of diabetes at a dose equal to or in excess of that providing a salutary effect in the diabetic somatic peripheral nervous system did not alter the severity of diabetes as assessed by plasma glucose level, 24-hurine volume, and levels of glycated hemoglobin. Chronic aminoguanidine therapy did not diminish the frequency or affect the ultrastructural appearance of neuroaxonal dystrophy in diabetic or age-matched control rat sympathetic ganglia after 7 or 10 months of continuous administration. Our findings (under these experimental conditions) do not support a role for aminoguanidine-sensitive processes in the development of sympathetic neuroaxonal dystrophy in diabetic rats. Glycation-linked aminoguanidine-insensitive processes, however, such as the formation of early glucose adducts (Schiff bases and Amadori products) withintra cellular and/or extracellular proteins and amine-containing lipids, superoxide anion generation during subsequent autoxidation of these glucoseadducts, and non-glycative processes, remain potential pathogenetic mechanisms for diabetic autonomic neuropathy.

L-fucose reduces collagen and noncollagen protein production in cultured cerebral microvessel endothelial cells.

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J Cell Physiol 1995 Dec;165(3):658-66

L-fucose is a monosaccharide which is present in low concentrations in normal serum but is increased in diabetes, cancer, and inflammatory diseases. The contribution that abnormal L-fucose levels make to the progression of these disorders is unknown. In a previous study we showed that increased L-fucose concentration reduced proliferation and proteoglycan production by cultured cerebral microvessel endothelial cells. In the present study we show that exposing cerebral microvessel endothelial cells for 2 weeks to medium containing an increased concentration of L-fucose causes a significant decrease in collagen and to a lesser extent noncollagen protein production. The effect of L-fucose on collagen and noncollagen protein production is concentration-dependent: 1 mM L-fucose causes a significant decrease in collagen production but has no effect on noncollagen protein production; a 5 mM L-fucose concentration causes a maximum decrease in both collagen and noncollagen protein production. This defect is unrelated to the reduction in myo-inositol uptake caused by L-fucose and is not prevented by aminoguanidine. Collagen production can be improved by restoring L-fucose-conditioned cells to normal medium. Culturing cells for 2 weeks in medium containing 10 mM L-fucose resulted in a 50% decrease in collagen production, which was restored to 75% of control after cells were transferred to normal medium for 7 days. In contrast, noncollagen protein production was totally restored after 3 days in normal medium. Increasing levels of L-fucose in serum of rats also resulted in a decrease in collagen production. Collagenase digestible in corporation of L-[2,3,4,5-3H]proline into protein of the articular cartilage from rats fed a diet containing 20% L-fucose for 3 weeks was reduced by about 40%compared to rats fed a normal diet. The decrease in collagen production in L-fucose fed rats was less than the reduction that occurred in streptozotocin-induced diabetic rats. These data suggest that changes in L-fucose concentration itself may be a factor in the regulation of collagen production.

Aminoguanidine does not inhibit the initial phase of experimental diabetic retinopathy in rats.

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Diabetologia (Germany) Mar 1995, 38 (3) p269-73

We have previously shown that long-term administration of aminoguanidine, an inhibitor of advanced glycosylation product formation, reduces the extent of experimental diabetic retinopathy in the rat by 85%. In order to determine whether the residual retinopathy that developed despite aminoguanidine was attributable to advanced glycation endproduct formation, a time-course study was performed in three different groups of male Wistar rats: non-diabetic controls (NC), streptozotocin-diabetic controls (DC) and streptozotocin-diabetic rats treated with aminoguanidine HCL, 50 mg/100 ml drinking water (D-AG). Eyes

were obtained at 24, 32, 44 and 56 weeks of diabetes/treatment duration and morphologic evaluation was done on retinal digest preparations. At 56 weeks, retinal basement membrane thickness was additionally measured. After 24 weeks of diabetes, the number of acellular capillaries was significantly elevated in DC (44.6 +/- 5.7/mm2 of retinal area, NC 19.6 +/- 4.9; $p < 0.001$) and increased continuously over time (DC56 weeks 87.4 +/- 15.1; $p < 0.001$ vs DC24 weeks). In contrast, acellular capillaries in D-AG increased over the first 24 weeks and then remained constant for the rest of the study (D-AG 24 weeks 35.7 +/- 5.18; $p < 0.01$ vs NC 24 weeks and NS vs DC 24 weeks; D-AG 56 weeks 42.0 +/- 6.20; p NS vsD-AG 24 weeks). (ABSTRACT TRUNCATED AT 250 WORDS)

Neurotoxicity of advanced glycation endproducts during focal stroke and neuroprotective effects of aminoguanidine.

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Proc Natl Acad Sci U S A (United States) Apr 25 1995, 92 (9) p3744-8

Cerebral infarction (stroke) is a potentially disastrous complication of diabetes mellitus, principally because the extent of cortical loss is greater in diabetic patients than in nondiabetic patients. The etiology of this enhanced neurotoxicity is poorly understood. We hypothesized that advanced glycation endproducts (AGEs), which have previously been implicated in the development of other diabetic complications, might contribute to neurotoxicity and brain damage during ischemic stroke. Using a rat model of focal cerebral ischemia, we show that systemically administered AGE-modified bovine serum albumin (AGE-BSA) significantly increased cerebral infarct size. The neurotoxic effects of AGE-BSA administration were dose- and time-related and associated with a paradoxical increase in cerebral blood flow. Aminoguanidine, an inhibitor of AGE cross-linking, attenuated infarct volume in AGE-treated animals. We conclude that AGEs may contribute to the increased severity of stroke associated with diabetes and other conditions characterized by AGE accumulation.

Nitric oxide synthesis and the effect of aminoguanidine and NG-monomethyl-L-arginine on the onset of diabetes in the spontaneously diabetic BB rat.

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Diabetes (United States) Mar 1995, 44 (3) p360-4

Nitric oxide (NO) synthesis and the effect of aminoguanidine (AG) and NG-monomethyl-L-arginine (NMMA) (inhibitors of NO synthase) on the onset of

diabetes were studied in the spontaneously diabetic BB rat. To measure in vivo NO production, 20 male 50-day-old diabetes-prone BB (BBdp) rats and age-matched non-diabetes-prone BB (BBn) rats were individually placed in metabolism cages. The animals had free access to a casein-based semipurified diet and deionized and double-distilled water. Urine excretion was collected every other day for 70 days, and urinary excretion of nitrate was measured as an index of in vivo NO synthesis. The urinary excretion of nitrate was enhanced by 150-200% in BBdp rats 4-6 days before the onset of diabetes, compared with aged-matched BBn rats. There was no difference in urinary excretion of nitrate between BBn rats and those BBdp rats that did not develop diabetes by the age of up to 120 days. To determine a role of NO in the development of spontaneous diabetes, 40-day-old male BBdp rats (30 rats per group) received daily subcutaneous injections of NMMA (acetate salt) (5 mg/kg body wt) or equal amounts of acetate (control) or oral administration of AG (0 or 3 g/l of drinking water) for 80 days. Both NMMA and AG delayed the onset of diabetes in BBdp rats by 13-15 days without altering the rate of incidence of diabetes.

The pharmacokinetics of aminoguanidine in end-stage renal disease patients on hemodialysis.

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Am J Kidney Dis (United States) Mar 1995, 25 (3) p420-5

Aminoguanidine is an investigational agent that may slow or prevent many diabetes-related complications. Since the elimination of aminoguanidine is dependent on renal function, its pharmacokinetics was investigated in eight chronic renal failure patients maintained on hemodialysis. Each patient received 300 mg of aminoguanidine hydrochloride during both an interdialytic and an intradialytic period. During the interdialytic period, the maximum aminoguanidine concentration (Cmax) and time to reach Cmax was 4.5 micrograms/mL and 1.5 hours, respectively. The terminal elimination hallife in these patients was prolonged (37.9 hours). The renal clearance was 2.1 mL/min. Only 8.7% of the administered dose was recovered unchanged in the urine, which is markedly reduced from what is recovered in urine in subjects with normal renal function. There was a positive correlation between the renal clearance of aminoguanidine and the patients' residual renal function ($P < 0.05$). During hemodialysis, the hallife of aminoguanidine was shortened to 3.9 hours. The hemodialysis clearance of aminoguanidine was 203.6 mL/min. After cessation of hemodialysis, a significant rebound in plasma aminoguanidine concentrations (mean, 39%) was observed. Thus, the dose of aminoguanidine hydrochloride will need to be significantly reduced in patients with end-stage renal disease. Given the interdialytic and intradialytic pharmacokinetics of aminoguanidine, three times weekly dosing after each hemodialysis session is suggested.

Effect of aminoguanidine on the impaired nitric oxide-mediated neurotransmission in anococcygeus muscle from diabetic rats.

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Neuropharmacology (England) Nov 1994, 33 (11) p1315-22

The contribution of advanced glycation end-product (AGE) formation to alterations in nitrergic neurotransmission caused by 8-week streptozotocin-induced diabetes has been examined in the rat anococcygeus muscle. Relaxant responses to nitrergic nerve stimulation (0.5-5 Hz, 10-sectrain), to nitric oxide (NO; 0.1-3 microM), to the NO donor, sodium nitroprusside (SNP; 5-500 nM), and to the cell-permeable analogue of cyclic guanosine monophosphate (cGMP), 8-bromo-cGMP (15 and 30 microM), were significantly smaller in muscles from diabetic rats than from control rats.Pretreatment with aminoguanidine hemisulphate (1 milligram drinking water) to inhibit AGE formation, did not alter the relaxant responses to nitrergic nerve stimulation, NO or SNP in tissues from control rats, or responses to NO or SNP in tissues from diabetic rats, however relaxations to nitrergic nerve stimulation were further reduced in tissues from diabetic rats. In anococcygeus muscles from untreated animals, a 20-min exposure to aminoguanidine (1 mM) in vitro had no effect on relaxations to nitrergic nerve stimulation. The results suggest that diabetes impairs nitrergic transmission in the rat anococcygeus at least partly through alterations in the cGMP-relaxation pathway. The impaired neurotransmission does not appear to be related to the formation of AGEs.

Interleukin 1 beta induces diabetes and fever in normal rats by nitric oxide via induction of different nitric oxide synthases.

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Cytokine (United States) Sep 1994, 6 (5) p512-20

Substantial in vitro evidence suggests that nitric oxide may be a major mediator of interleukin 1 (IL-1) induced pancreatic beta-cell inhibition and destruction in the initial events leading to insulin-dependent diabetes mellitus. Using NG-nitro-L-arginine methyl ester, an inhibitor of both the constitutive and the cytokine inducible forms of nitric oxide synthase, andaminoguanidine, a preferential inhibitor of the inducible form of nitric oxide synthase, we investigated the impact of inhibiting nitric oxide production on food-intake, body weight and temperature, blood glucose,plasma insulin, glucagon, corticosterone and leukocyte- and differential-counts in normal rats injected once daily for 5 days with interleukin 1 beta (IL-1 beta) (0.8 microgram/rat = 4.0 micrograms/kg). Inhibition of both the constitutive and the inducible forms of nitric oxide synthase prevented IL-1 beta-

induced fever, hyperglycaemia, hypoinsulinemia, and hyperglucagonemia, and partially prevented lymphopenia and neutrophilia, but had no effect on IL-1 beta-induced anorexia and changes in plasma corticosterone. Preferential inhibition of the inducible form of nitric oxide synthase using two daily injections of 5 mg/rat of aminoguanidine prevented IL-1 beta-induced hyperglycaemia and hypoinsulinaemia, and slightly reduced the pyrogenicity of IL-1 on 3 out of 5 days. Higher doses of aminoguanidine (100 mg/rat) prevented lymphopenia and neutrophilia. We conclude that nitric oxide produced by the inducible form of nitric oxide synthase, mediates the IL-1 beta-induced inhibition of insulin release and that the effect of IL-1 beta on temperature, pancreatic alpha-cells, and leukocyte differential counts seems to be mediated by nitric oxide produced by the constitutive form of nitric oxide synthase.

The reaction of methylglyoxal with aminoguanidine under physiological conditions and prevention of methylglyoxal binding to plasma proteins.

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Biochem Pharmacol (England) Nov 16 1994, 48 (10) p1865-70

Increased formation of methylglyoxal in clinical diabetes mellitus and metabolism by the glyoxalase system has been linked to the development of clinical complications of diabetes: retinopathy, neuropathy and nephropathy. Aminoguanidine has been proposed as a prophylactic agent for preventive therapy of diabetic complications. Methylglyoxal reacted with aminoguanidine under physiological conditions to form two isomerictriazines, 3-amino-5-methyl-1,2,4-triazine and 3-amino-6-methyl-1,2,4-triazine. The mean second order rate constant for the reaction of methylglyoxal with aminoguanidine, kMG.AG = 0.39 +/- 0.06 M-1 sec-1 at pH 7.4 and 37degrees. Under these conditions, no methylglyoxal bisguanylhydrazone was detected. Aminoguanidine prevented the irreversible modification of human plasma protein by a physiological concentration of methylglyoxal (1microM); the median inhibitory concentration IC50 value of aminoguanidine was 203 +/- 16 microM (N = 28). The scavenging of methylglyoxal by aminoguanidine may contribute to the beneficial effects of aminoguanidine in the prevention of vascular pathogenesis in diabetes.

Advanced glycation end products induce glomerular sclerosis and albuminuria in normal rats.

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Proc Natl Acad Sci U S A (United States) Nov 22 1994, 91 (24) p11704-8

High levels of tissue advanced glycation end products (AGEs) that result from the spontaneous modification of proteins by glucose occur in diabetes and aging. To address the potential pathogenic role of AGEs in the glomerulosclerosis of diabetes or nephrosclerosis of aging, doses of AGE-modified rat albumin (25 mg per kg per day, i.v.) sufficient to elevate circulating AGE levels to the range of diabetic serum were administered daily to healthy rats alone or in combination with the AGE inhibit oraminoguanidine. After 5 months, the AGE content of renal tissues in AGE-treated rats rose to 50% above controls ($P < 0.025$), whereas serum contained 2.8-fold greater AGE levels ($P < 0.025$). Light and electronmicroscopy of kidneys from AGE-treated rats revealed a more than 50% increase in glomerular volume compared to controls ($P < 0.001$), significant periodic acid/Schiff reagent-positive deposits, basement membrane widening, and mesangial extracellular matrix increase and indicated significant glomerulosclerosis compared to untreated ($P < 0.002$) or albumin-treated controls ($P < 0.002$). These changes were associated with significant loss of protein ($P < 0.005$) and albumin ($P < 0.002$) in the urine of AGE-treated rats compared to controls. Cotreatment with aminoguanidine markedly limited both the structural and functional defects. These in vivo data demonstrate that AGEs influence glomerular structure and function in a manner leading to glomerulosclerosis. The effects are AGE-specific, as they are ameliorated by a pharmacological AGE inhibitor, aminoguanidine.

Active and passive mechanical properties of isolated arterioles from STZ-induced diabetic rats. Effect of aminoguanidine treatment.

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Diabetes (United States) Dec 1994, 43 (12) p1450-6

Studies were performed to examine the effect of experimental diabetes (4-6 weeks duration) on both the passive elastic and active myogenic properties of isolated skeletal muscle arterioles. Studies were conducted on untreated streptozotocin (60 mg/kg)-induced diabetic rats and in similar rats treated daily with either amino-guanidine (25 mg/kg) ormethylguanidine (25 mg/kg). First-order cremaster muscle arterioles were isolated, cannulated, and pressurized in the absence of intraluminal flow.Video microscopy was used to determine relationships between arteriolar diameter and intraluminal pressure both in the active and passive (o mmol/lCa(2+)-2 mmol/l EGTA superfusated) tes. The measurements were used to calculate active myogenic responses, arteriolar distensibility, and stress-strain relationships. Under passive conditions, arterioles from untreated diabetic animals appeared to be stiffer and less distensible compared with similar arterioles from control animals. Under active conditions, i.e., in the presence of extracellular Ca2+, arterioles from the untreated diabetic group showed impaired myogenic reactivity as evidenced by a significant ($P < 0.001$) reduction in the negative slope of the pressure-diameter relationship over a physiological range of intraluminal pressures. Chronic treatment with aminoguanidine prevented the diabetes-induced changes in the active and passive properties of the isolated arterioles while

treatment with methylguanidine appeared ineffective. Vasodilator responses to topically applied acetylcholine (10(-8) to 5 x 10(-6) mol/l) were significantly impaired in diabetic animals irrespective of treatment with aminoguanidine. The data indicate that experimental diabetes is associated with a decreased passive distensibility, or stiffening, of skeletal muscle arterioles that, in addition, may contribute to impaired active myogenic responses.

Effects of aminoguanidine on insulin release from pancreatic islets.

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Endocr J (England) Jun 1994, 41 (3) p309-13

Aminoguanidine (AG) is a potential therapeutic agent for preventing the generation of advanced glycation end products in diabetes mellitus. In this study, the effect of AG on insulin secretion was investigated in in vitro rat pancreatic islets. The islets were aseptically isolated and cultured in tissue culture medium 199 for 48 h with or without AG. After the culture, batches of 10 islets were incubated in Krebs-Ringer bicarbonate buffer containing 3.3 mM or 16.7 mM glucose. Islets previously exposed to 0.18 mM AG or 0.45 mM AG showed similar insulin release to control islets at a 16.7 mM glucose concentration, but high glucose-stimulated insulin release was inhibited in the islets exposed to 1.8 mM. In the perifusion experiment, insulin release caused by 16.7 mM glucose from the islets previously exposed to 1.8 mM AG was not significantly different from that of the control islets. However, culture of the islets with higher AG concentrations, 4.55 mM and 9.1 mM, significantly inhibited glucose-stimulated insulin release (< 0.02 and 0.002, respectively). These results suggest that AG at high concentrations impairs pancreatic B-cell response to a high concentration of glucose.

TNF-alpha and IFN-gamma potentiate the deleterious effects of IL-1 beta on mouse pancreatic islets mainly via generation of nitric oxide.

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Cytokine (United States) Jul 1994, 6 (4) p399-406

Cytokines may be important mediators of beta-cell damage in early insulin-dependent diabetes mellitus. In order to further characterize the mechanism(s) of action of cytokines on insulin-producing cells, mouse pancreatic islets were exposed for 48 h to IL-1 beta, IFN-gamma or TNF-alpha, alone or in combinations. The three cytokines induced islet nitric oxide (NO) production, an effect most marked when islets were exposed to the three cytokines together. In parallel with NO production, IL-1 beta+IFN-gamma+TNF-alpha impaired islet function, as judged by decreased islet DNA and insulin content, decreased

glucose metabolism and decreased glucose-induced insulin release. Aminoguanidine, an inhibitor of NO production, prevented all the above described suppressive effects of the cytokines, with exception of depletion in islet insulin content. In parallel experiments, insulin-producing RIN cells were exposed for 6 h to the same cytokines. Both IL-1 beta and TNF-alpha, but not IFN-gamma, induced NO production and expression of the mRNA encoding for the inducible form of the enzyme NO synthase (iNOS). These effects were most pronounced when combinations of IL-1 beta+IFN-gamma or IL-1 beta+IFN-gamma+TNF-alpha were used. As a whole, the data suggest that combinations of cytokines induce higher amounts of NO generation by mouse pancreatic islets than each of the cytokines isolated. An important source of islet NO production are probably the beta-cells, as pointed by data obtained with an insulinoma cell line. Most of the deleterious effects of the cytokines of mouse islets are prevented by blocking NO production, suggesting that NO is the main mediator of cytokine-induced beta-cell damage.

Creatine reduces collagen accumulation in the kidneys of diabetic db/db mice.

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Nephron (Switzerland) 1994, 67 (2) p214-7

In the present study, we tested the hypothesis whether creatine, a metabolite of arginine metabolism, shares the pharmacological activities of arginine reducing collagen accumulation in the diabetic kidney. Ten db/db mice were given, for 3 months, a solution containing a daily dosage of creatine of 50 mg/kg body weight. Eleven db/db mice served as controls. At the end of the 3-month study period, the mean N-carboxymethyllysine concentration in the untreated group was significantly higher than in the treated group (0.163 +/- 0.18 versus 0.096 +/- 0.017 nmol/mumol hydroxyproline, $p < 0.001$). Collagen accumulation was also significantly higher in the untreated than in the treated group (2.21 +/- 0.24 versus 1.68 +/- 0.22 mumol hydroxyproline/100 mg kidney weight, $p < 0.001$). We conclude that creatine led to a significant reduction in collagen type IV accumulation resembling arginine or aminoguanidine action. We do suggest that the guanidino group common to both compounds is able to block reactive carbonyls.

L-arginine reduces heart collagen accumulation in the diabetic db/db mouse.

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Circulation (United States) Jul 1994, 90 (1) p479-83

BACKGROUND: Diabetic cardiomyopathy presents with significant collagen accumulation; decreased solubility, increased glucose-mediated abnormal cross-linking, free radical cross-linking, or glucose-induced increased transcription of collagen is incriminated. In a previous study, we reducedcollagen accumulation in the kidneys of diabetic mice by treatment with oral arginine. This observation led us to examine the effect of arginine oncardial fibrosis.

METHODS AND RESULTS: Twenty-nine db/db spontaneouslydiabetic mice were used in the experiments. Sixteen were given L-arginine(free base, in tap water, 50 mg/kg body wt per day) for 4 months. At theend of the experiment, we determined total collagen content of total ventricular tissue, acid solubility, carboxymethyllysine, O-tyrosine, glutathione, blood glucose, and fructosamine as parameters for glycemic control. Heart collagen level was significantly (P = .0001) reduced in the experimental group (mean, 0.24 +/- 0.05) compared with the control group (mean, 0.49 +/- 0.10 mumol hydroxyproline per 100 mg heart tissue). Significantly more collagen could be eluted from heart samples of the experimental group (P = .02). Carboxymethyllysine and O-tyrosine did not differ when related to heart weight. Glutathione level was significantly higher in the untreated group (P = .003). Parameters of glycemic control did not differ between the groups.

CONCLUSIONS: Our findings clearly indicate that L-arginine reduced total heart collagen and increased acid solubility of heart collagen. Both findings are compatible with the cross-linking hypothesis. The data for carboxymethyllysine, O-tyrosine, and glutathione would rule out the glycoxidation hypothesis and, therefore, free radical cross-linking. The postulated mechanism of action is most likely the blocking of reactive carbonyl functions by L-arginine in analogyto amino guanidine activity. Correlations of collagen with glycemic control, however, point to an association of glucose with collagen metabolism, a phenomenon documented in cell cultures at the transcriptional level.

Cytokines suppress human islet function irrespective of their effects on nitric oxide generation.

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J Clin Invest (United States) May 1994, 93 (5) p1968-74

Cytokines have been proposed as inducers of beta-cell damage in human insulin-dependent diabetes mellitus via the generation of nitric oxide (NO). This concept is mostly based on data obtained in rodent pancreatic islets using heterologous cytokine preparations. The present study examined whether exposure of human pancreatic islets to different cytokines induces NO and impairs beta-cell function. Islets from 30 human pancreata were exposed for 6-144 h to the following human recombinant cytokines, alone or in combination: IFN-gamma (1,000 U/ml), TNF-alpha (1,000 U/ml), IL-6 (25U/ml), and IL-1 beta (50 U/ml). After 48 h, none of

the cytokines alone increased islet nitrite production, but IFN-gamma induced a 20% decrease in glucose-induced insulin release. Combinations of cytokines, notably IL-1beta plus IFN-gamma plus TNF-alpha, induced increased expression of inducible NO synthase mRNA after 6 h and resulted in a fivefold increase in medium nitrite accumulation after 48 h. These cytokines did not impair glucose metabolism or insulin release in response to 16.7 mM glucose, but there was an 80% decrease in islet insulin content. An exposure of 144 h toIL-1 beta plus IFN-gamma plus TNF-alpha increased NO production and decreased both glucose-induced insulin release and insulin content. Inhibitors of NO generation, aminoguanidine or NG-nitro-L-arginine, blocked this cytokine-induced NO generation, but did not prevent the suppressive effect of IL-1 beta plus IFN-gamma plus TNF-alpha on insulin release andcontent. In conclusion, isolated human islets are more resistant to thesuppressive effects of cytokines and NO than isolated rodent islets. Moreover, the present study suggests that NO is not the major mediator of cytokine effects on human islets.

Amelioration of dermal lesions in streptozotocin-induced diabetic rats by aminoguanidine.

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Diabetes Res (Scotland) 1992, 20 (4) p87-95

As aminoguanidine (AG) is known to prevent non-enzymatic glycosylation in various tissues, we have histologically and biochemically evaluated AG effects on the skin in control, SZ-diabetic and AG-treated (25 mg/kgbw/day, 10w) diabetic rats. HbA1c and plasma glucose levels in diabetic andAG-treated diabetic rats were maintained about two times higher than those in control rats during the 10 weeks of the experiment. Histological findings revealed that the dermis in diabetic rats was thin and edematous, associated with swelling and degeneration of collagen fibers. Necrobiotic changes were seen in the lower dermis. These changes were greatly improved in AG-treated diabetic rats. Skin glucose contents in diabetic andAG-treated diabetic rats were about 10 times higher than those in the controls, whereas there was no difference in the sorbitol contents between three groups. Dry weight of the skin and collagen content was wellcorrelated (r = 0.9044) and collagen represented 78.0 +/- 2.3% of the dryweight. By SDS-PAGE analysis of cyanogen bromide digests it was shown that high molecular weight peptides were increased in diabetic rats, but were decreased in AG-treated diabetic rats. The mean of glycosaminoglycan (GAG) contents of diabetic skin was 54% of that in the controls (1.58 +/- 0.09vs. 2.94 +/- 0.39 micrograms/mg dry weight, $P < 0.0025$), which increased significantly in AG-treated diabetic rats (1.75 +/- 0.07 microgram/mg dryweight, $P < 0.01$ vs. diabetic).

Glycation, glycoxidation, and cross-linking of collagen by glucose. Kinetics, mechanisms, and inhibition of late stages of the Maillard reaction.

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Diabetes (United States) May 1994, 43 (5) p676-83

The Maillard or browning reaction between sugar and protein contributes to the increased chemical modification and cross-linking of long-lived tissue proteins in diabetes. To evaluate the role of glycation and oxidation in these reactions, we have studied the effects of oxidative and antioxidative conditions and various types of inhibitors on the reaction of glucose with rat tail tendon collagen in phosphate buffer at physiological pH and temperature. The chemical modifications of collagen that were measured included fructoselysine, the glycoxidation products Nepsilon-(carboxymethyl) lysine and pentosidine and fluorescence. Collagen cross-linking was evaluated by analysis of cyanogen bromide peptides using sodium dodecyl sulfate-polyacrylamide gel electrophoresis and by changes in collagen solubilization on treatment with pepsin or sodium dodecylsulfate. Although glycation was unaffected, formation of glycoxidation products and cross-linking of collagen were inhibited by antioxidative conditions. The kinetics of formation of glycoxidation products proceeded with a short lag phase and were independent of the amount of Amadori adduct on the protein, suggesting that autoxidative degradation of glucose was a major contributor to glycoxidation and cross-linking reactions. Chelators, sulfhydryl compounds, antioxidants, and aminoguanidine also inhibited formation of glycoxidation products, generation of fluorescence, and cross-linking of collagen without significant effect on the extent of glycation of the protein. We conclude that autoxidation of glucose or Amadori compounds on protein plays a major role in the formation of glycoxidation products and cross-liking of collagen by glucose in vitro and that chelators, sulfhydryl compounds, antioxidants, and aminoguanidine act as uncouplers of glycation from subsequent glycoxidation and cross-linking reactions.

Aminoguanidine inhibits the development of accelerated diabetic retinopathy in the spontaneous hypertensive rat.

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Diabetologia (Germany) Jan 1994, 37 (1) p32-5

Arterial hypertension has been identified as a major secondary risk factor for diabetic retinopathy. However, the mechanisms by which hypertension worsens retinopathy are unknown. Inhibition of advanced glycation product formation prevents the development of experimental diabetic retinopathy in normotensive diabetic rats. In this study the effect of hypertension on the rate of diabetic retinopathy development and the formation of arteriolar thrombosis was

evaluated. We also evaluated the effect of aminoguanidine, an inhibitor of advanced glycation and product formation on retinal pathology of diabetic hypertensive rats. After 26 weeks of diabetes, hypertension accelerated the development of retinopathy despite a lower mean blood glucose level than in the non-hypertensive group (diabetic spontaneous hypertensive rats (SHR) 16.00 +/- 6.83 mmol/l; diabetic normotensive Wistar Kyoto rats (WKY) 34.9 +/- 3.64 mmol/l; p <0.0001). Diabetic SHR had nearly twice as many acellular capillaries as diabetic WKY (SHR diabetic: 91.9 +/- 7.5 acellular capillaries per mm2 of retinal area vs WKY diabetic: 53.7 +/- 8.5 acellular capillaries per mm2 of retinal area), and a 3.8-fold increase in the number of arteriolar microthromboses (SHR diabetic 23,504 +/- 5523 microns2 vs SHR non-diabetic 6228 +/- 2707 microns2). Aminoguanidine treatment of SHR diabetic rats reduced the number of acellular capillaries by 50%, and completely prevented both arteriolar deposition of PAS-positive material and abnormal microthrombus formation. These data suggest that hypertension-induced deposition of glycated proteins in the retinal vasculature plays a central role in the acceleration of diabetic retinopathy by hypertension.

Aminoguanidine reduces regional albumin clearance but not urinary albumin excretion in streptozotocin-diabetic rats.

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Diabetologia (Germany) Jan 1994, 37 (1) p10-4

Advanced glycation end-product-formation is thought to play a role in the development of diabetic angiopathy. By altering the structure of different extracellular matrix components advanced glycation end-products might affect vascular and glomerular permeability. In this study we investigated the effect of treatment with an inhibitor of advanced glycation end-product-formation, aminoguanidine, on vascular permeability and the development of albuminuria in streptozotocin-induced diabetic rats. Male Wistar Rp rats were randomized into a control group, a diabetic group, and an aminoguanidine-treated diabetic group. After 8 weeks, 24-h urine collections were taken and rats were implanted with an arterial and avenous catheter. mean arterial blood pressure was determined by intra-arterial measurement. Regional albumin clearances were assessed in the eye, ileum, lung, skeletal muscle and skin using an isotope technique. Mean arterial pressure in the diabetic group was significantly lower in the control and aminoguanidine-treated groups ($p < 0.02$). Regional albumin clearances were significantly increased in all tissues of diabetic rats compared to control rats ($p < 0.05$). Aminoguanidine treatment of diabetic rats resulted in a significant decrease of regional albumin clearance in all tissues except the lung ($p < 0.05$, lung $p = 0.07$). The development of albuminuria in diabetic rats however, was not affected by aminoguanidine.

Aminoguanidine: a drug proposed for prophylaxis in diabetes inhibits catalase and generates hydrogen peroxide in vitro.

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Biochem Pharmacol (England) Oct 5 1993, 46 (7) p1139-44

Aminoguanidine (AG) has been proposed as a drug of potential benefit in prophylaxis of the complications of diabetes. We show here that AG irreversibly inhibits catalase with an efficacy similar to aminotriazole. AG also produces hydrogen peroxide, in a transition metal-catalysed process which may be partially dependent upon prior hydrolysis of AG to semicarbazide and hydrazine. These observations may be of importance in proposals for the long term administration of AG in diabetes.

Nitric oxide production in islets from nonobese diabetic mice: aminoguanidine-sensitive and -resistant stages in the immunological diabetic process.

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Proc Natl Acad Sci U S A (United States) Oct 1 1993, 90 (19) p8992-5

The role of nitric oxide (NO.) in the development of immunologically induced diabetes was examined. Transfer of spleen cells obtained from diabetic female nonobese diabetic (NOD) mice to nondiabetic irradiated males induced diabetes 11-13 days after transfer. Islets isolated from recipient male mice produced NO. in a time-dependent fashion. The production of nitrite was initially detected at day 6 after transfer, with increasing levels by days 9 and 13. Under similar conditions glucose-induced insulin secretion by isolated NOD mouse islets was irreversibly reduced by approximately 40% at days 6, 9, and 13 after transfer of spleen cells. The number of islets harvested per pancreas by the 9th and 13th day after transfer was decreased by 20-25% as compared to controls. Treatment of male NOD mice with aminoguanidine, an inhibitor of the inducible form of NO. synthase, reduced the production of NO. in islets and delayed the development of diabetes by 3-8 days. The temporary inhibition by aminoguanidine was dependent on both inhibitor concentration and number of spleen cells transferred. These results indicate that NO. is produced in NOD islets as a result of an immunological diabetogenic process and suggests a role of this compound in the immunological diabetic process.