

DIABETES SUPPORT NUTRIENTS-Research Abstracts

	Metabolic Formula	Chromium Synergy	Lipoic Synergy /Supreme	DFH product
Biotin	O	O	O	
Carnosine				Carnosine
Carotenoids				Ultimate Antioxidant
Chromium	O	O		TDM
Copper	O			TDM
COQ10				Q-Avail
Folic	O			B-Supreme, Super Liquid Folate
Green tea				TAD Ao, Ult AO
Inositol	O			Inositol
Lipoic Acid			O	
Magnesium	O			Magnesium chelates
Manganese	O	O		TDM
Niacinamide	O			
Omega-3				Omega Synergy, Omega Marine
GLA				Omega Synergy, GLA
Pantethine	O			
Pantothenic	O			B Supreme
Potassium	O			potassium Kreb chelates
Selenium	O			TDM, TAD Antioxidant
Taurine	O	O	O	Taurine
Thiamin	O			B Supreme
Vandium	O	O		
Vit D		O		Genuine Arctic Cod Liver Oil, TDM
Vitamin B12	O			B Supreme
Vitamin B6	O			B Supreme
Vitamin C	O			Stellar C
Vitamin E				Vit E mixed tocopherols
Zinc	O	O		Zinc Supreme, Zinc Challenge

Biotin-1

Bender DA..Optimum nutrition: thiamin, biotin and pantothenate. Proc Nutr Soc. 1999 May;58(2):427-33.

The metabolism of glucose is deranged in thiamin deficiency, but once any deficiency has been corrected there is no further effect of increased thiamin intake on the ability to metabolize glucose through either pyruvate dehydrogenase (EC 1.2.4.1) and the citric acid cycle, or the pentose phosphate pathway, in which transketolase (EC 2.2.1.1) is the thiamin-dependent step. It has been suggested that the Wernicke-Korsakoff syndrome is associated with a genetic variant of transketolase which requires a higher than normal concentration of thiamin diphosphate for activity. This finding would suggest that there may be a group of the population who have a higher than average requirement for thiamin, but the evidence is not convincing. There are no estimates of biotin requirements, but either coenzyme saturation of erythrocyte pyruvate carboxylase, or the excretion of 3-hydroxy-isovalerate (perhaps after a test dose of leucine) could be used to assess requirements in depletion-repletion studies. **Biotin deficiency leads to impaired glucose tolerance**, but it is unlikely that glucose tolerance could be used to assess optimum biotin status, since other more common factors affect glucose tolerance to a greater extent. **Plasma triacylglycerol and nonesterified fatty acids are moderately elevated in pantothenic acid deficiency**. However, this is unlikely to be useful in assessing pantothenate status, since again, other more common factors affect plasma lipids. To date there are no biochemical indices of adequate pantothenate nutrition, and no estimates of requirements.

Carnosine-1.

Ann N Y Acad Sci. 2002 Apr;959:285-94.

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Full text article at
www.annalsnyas.org

Reaction of carnosine with aged proteins: another protective process?

Hipkiss AR, Brownson C, Bertani MF, Ruiz E, Ferro A.

GKT School of Biomedical Sciences, King's College London, Guy's Campus, London Bridge, London SE1 1UL, United Kingdom. alan.hipkiss@kcl.ac.uk

Cellular aging is often associated with an increase in protein carbonyl groups arising from oxidation- and glycation-related phenomena and suppressed proteasome activity. These "aged" polypeptides may either be degraded by 20S proteasomes or cross-link to form structures intractable to proteolysis and inhibitory to proteasome activity. Carnosine (beta-alanyl-L-histidine) is present at surprisingly high levels (up to 20 mM) in muscle and nervous tissues in many animals, especially long-lived species. Carnosine can delay senescence in cultured human fibroblasts and reverse the senescent phenotype, restoring a more juvenile appearance. As better antioxidants/free-radical scavengers than carnosine do not demonstrate these antisenescent effects, additional properties of carnosine must contribute to its antisenescent activity. Having shown that carnosine can react with protein carbonyls, thereby generating "carnosinylated" polypeptides using model systems, we propose that similar adducts are generated in senescent cells exposed to carnosine. Polypeptide-carnosine adducts have been recently detected in beef products that are relatively rich in carnosine, and carnosine's reaction with carbonyl functions generated during amino acid deamidation has also been described. Growth of cultured human fibroblasts with carnosine stimulated proteolysis of long-labeled proteins as the cells approached their "Hayflick limit," consistent with the idea that carnosine ameliorates the senescence-associated proteolytic decline. We also find that carnosine suppresses induction of heme-oxygenase-1 activity following exposure of human endothelial cells to a glycated protein. The antisenescent activity of the spin-trap agent alpha-phenyl-N-t-butylnitron (PBN) towards cultured human fibroblasts resides in N-t-butyl-hydroxylamine, its hydrolysis product. As hydroxylamines are reactive towards aldehydes and ketones, the antisenescent activity of N-t-butyl-

hydroxylamine and other hydroxylamines may be mediated, at least in part, by reactivity towards macromolecular carbonyls, analogous to that proposed for carnosine.

Carnosine 2

Biochemistry (Mosc). 2000 Jul;65(7):771-8.

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Biochemistry (Moscow)
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Carnosine and protein carbonyl groups: a possible relationship.

Hipkiss AR.

Division of Biomolecular Sciences, GKT School of Biomedical Sciences, King's College London, London SE1 1UL, UK. alan.hipkiss@kcl.ac.uk.

Carnosine has been shown to react with low-molecular-weight aldehydes and ketones and has been proposed as a naturally occurring anti-glycating agent. It is suggested here that carnosine can also react with ("carnosinylate") proteins bearing carbonyl groups, and evidence supporting this idea is presented. Accumulation of protein carbonyl groups is associated with cellular ageing resulting from the effects of reactive oxygen species, reducing sugars, and other reactive aldehydes and ketones. Carnosine has been shown to delay senescence and promote formation of a more juvenile phenotype in cultured human fibroblasts. It is speculated that carnosine may intracellularly suppress the deleterious effects of protein carbonyls by reacting with them to form protein-carbonyl-carnosine adducts, i.e., "carnosinylated" proteins. Various fates of the carnosinylated proteins are discussed including formation of inert lipofuscin and proteolysis via proteasome and RAGE activities. It is proposed that the anti-ageing and rejuvenating effects of carnosine are more readily explainable by its ability to react with protein carbonyls than its well-documented antioxidant activity.

Carotenoids-1

Indian J Exp Biol. 1999 Apr;37(4):399-401.

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Effect of betacarotene on protein glycosylation in alloxan induced diabetic rats.

Aruna RV, Ramesh B, Kartha VN.

Department of Biochemistry, P.S.G. Institute of Medical Sciences & Research, Peelamedu, Coimbatore, India.

Free radicals are increasingly formed in diabetes mellitus by the auto oxidation of glucose and glycosylated proteins. Oxidative stress and proteinglycosylation are closely related processes and have been shown to contribute to the development of complications in diabetes mellitus. The extent of protein glycosylation was assessed in alloxan induced diabetic rats after being treated with 50 mg of betacarotene for 40 days. The level of fructosamine and glycosylated haemoglobin was comparison with non treated diabetic rats. The results indicate the beneficial role of betacarotene in reducing diabetic complications like glycosylation in experimental diabetic rats.

Chromium-1

Med Sci Sports Exerc. 1997 Aug;29(8):992-8.

[Related Articles, Links](#)

Chromium and exercise training: effect on obese women.

Grant KE, Chandler RM, Castle AL, Ivy JL.

Department of Kinesiology and Health Education, University of Texas at Austin 78712, USA.

Chromium supplementation may affect various risk factors for coronary artery disease (CAD) and non-insulin-dependent diabetes mellitus (NIDDM), including body weight and composition, basal plasma hormone and substrate levels, and response to an oral glucose load. This study examined the effects of chromium supplementation (400 micrograms.d-1), with or without exercise training, on these risk factors in young, obese women. Chromium picolinate supplementation resulted in significant weight gain in this population, while exercise training combined with **chromium nicotinate supplementation resulted in significant weight loss and lowered the insulin response to an oral glucose load.** We conclude that high levels of chromium picolinate supplementation are contraindicated for weight loss in young, obese women. Moreover, our results suggest that exercise training combined with chromium nicotinate supplementation may be more beneficial than exercise training alone for modification of certain CAD and NIDDM risk factors.

Chromium-2

Diabetes Res Clin Pract. 1995 Jun;28(3):179-84.

[Related Articles, Links](#)



Price: US \$ 30.00

Effects of chromium supplementation on fasting insulin levels and lipid parameters in healthy, non-obese young subjects.

Wilson BE, Gondy A.

Department of Internal Medicine, University of Nevada School of Medicine, Las Vegas 89102, USA.

Trivalent chromium is an essential trace element for normal carbohydrate metabolism and insulin sensitivity. Because of this biological activity, chromium supplementation has been studied as a potential therapy of insulin resistant states and dyslipidemias, and has been promoted as a health aid to the general population. To determine if there is a risk of subclinical chromium deficiency in young, otherwise healthy adults, we evaluated the effect of chromium supplementation, versus placebo, on insulin levels and serum lipids in a double-blind, randomized trial in 26 young adults (mean age 36 years). Fasting levels of glucose, immunoreactive insulin (IRI), and lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) were measured before and after 90 days of daily supplementation with a chromium (III)-nicotinate preparation, containing 220 micrograms elemental chromium, or placebo. There were no statistically significant differences in the percentage change of fasting glucose, IRI or lipids between the chromium (n = 15) and placebo (n = 11) groups after 90 days of supplementation. However, those individuals within the chromium group with initial fasting IRI levels greater than 35 pmol/l had a significant decrease in IRI level after supplementation (P < 0.03) despite no significant changes in serum lipids. These subjects may benefit from chromium supplementation by improving insulin sensitivity and cardiovascular risk over time.

Chromium-3

Metabolism. 1987 Sep;36(9):896-9.

[Related Articles, Links](#)

Evidence for synergism between chromium and nicotinic acid in the control of glucose tolerance in elderly humans.

Urberg M, Zemel MB.

Impaired glucose tolerance results from Cr restriction in animals, and Cr supplementation improves glucose tolerance in diabetic animals. These effects are presumably due to the role of Cr in glucose tolerance factor

(GTF), a complex of Cr and nicotinic acid believed to facilitate insulin binding. Humans, however, do not uniformly respond to Cr supplementation. The present study was designed to evaluate the possibility that the failure results from inadequate levels of dietary nicotinic acid to serve as substrate for GTF synthesis. Sixteen healthy elderly volunteers were divided into three groups and given either 200 micrograms Cr, 100 mg nicotinic acid, or 200 micrograms Cr + 100 mg nicotinic acid daily for 28 days and evaluated on days 0 and 28. Fasting glucose and glucose tolerance were unaffected by either chromium or nicotinic acid alone. In contrast, the combined chromium-nicotinic acid supplement caused a 15% decrease in a glucose area integrated total (p less than .025) and a 7% decrease in fasting glucose. None of the treatments exerted any effect on fasting or one-hour insulin levels. Thus, these data suggest that the inability to respond to chromium supplementation may result from suboptimal levels of dietary nicotinic acid.

Chromium-4

Clin Nephrol. 1997 May;47(5):325-30.

[Related Articles, Links](#)

Effects of different chromium compounds on blood pressure and lipid peroxidation in spontaneously hypertensive rats.

Preuss HG, Grojec PL, Lieberman S, Anderson RA.

Dept. of Medicine, Georgetown University Medical Center, Washington, DC 2007, USA.

In a previous study, we found that oral chromium nicotinate overcame sucrose-induced hypertension in spontaneously hypertensive rats (SHR). Accordingly, we examined more chromium compounds to determine if others were more or less effective in regulating blood pressure (BP) of SHR. Since chromium is postulated to be an antioxidant, we also assessed the ability of different chromium compounds to alter free radical formation measured by determining thiobarbituric acid reactive substances (TBARS). The control group of SHR ingested a diet low in chromium, and 5 other groups ate the same diet with various chromium compounds added at 5 ppm-chloride, acetate, nicotinic acid-glycine-cysteine-glutamic acid (NA-AA), picolinate, and nicotinate. Following this, the rats were challenged with drinking water containing 5% and 10% w/v sucrose. Except for NA-AA, all chromium compounds inhibited the sucrose-induced elevation of systolic BP; and acetate, picolinate, and nicotinate chromium compounds lowered HbA1C below control. Only chromium acetate and nicotinate significantly lowered both hepatic and renal TBARS. Chromium picolinate lowered hepatic TBARS, and chromium chloride and NA-AA lowered neither. We conclude that chromium, rather than a specific ligand, plays a major role in ameliorating sucrose-induced BP elevations and can act as an antioxidant.

Chromium-5

Ann N Y Acad Sci. 2002 May;957:250-9.

[Related Articles, Links](#)

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US\$8.00

Protective effects of a novel niacin-bound chromium complex and a grape seed proanthocyanidin extract on advancing age and various aspects of syndrome X.

Preuss HG, Bagchi D, Bagchi M.

Department of Physiology, Georgetown University Medical Center, Washington, D.C. 20007, USA.
preusshg@georgetown.edu

Aging is the progressive accumulation of changes with time that are responsible for the ever-increasing likelihood of disease and death. The precise cascade of pathological events mainly responsible for aging are still not clearly understood, but enhanced production of free radicals and its deleterious effects on proteins, nucleic

acids, and fats, as well as enhanced glycosylation of proteins and DNA are prevalent during aging. Insulin resistance may be a common etiology, at least in part, behind the pathobiological alterations of advancing age. Prevalent age-related disorders such as cardiovascular diseases, obesity, and cancer have been associated with impaired glucose/insulin metabolism and its consequences. This leads to future strategies to combat the aging process and chronic disorders such as the components of syndrome X associated with aging. Increasing the intake of antioxidants and/or substances recognized to enhance insulin sensitivity is a natural means of combatting the glucose/insulin perturbations and free radical damage. Accordingly, ingestion of niacin-bound chromium and natural antioxidants such as grape seed proanthocyanidin extract has been demonstrated to improve insulin sensitivity and/or ameliorate free radical formation and reduce the signs/symptoms of chronic age-related disorders including syndrome X. These natural strategies possess a highly favorable risk/benefit ratio.

Chromium-6

J Trace Elem Med Biol. 1999 Jul;13(1-2):57-61.

[Related Articles, Links](#)

Chromium homeostasis in patients with type II (NIDDM) diabetes.

Morris BW, MacNeil S, Hardisty CA, Heller S, Burgin C, Gray TA.

Department of Clinical Chemistry, Northern General Hospital Trust, Sheffield, South Yorkshire, U.K.

The purpose of this study was to assess chromium handling in non-insulin dependent diabetic patients (NIDDM) compared to healthy volunteers. Chromium handling was evaluated using fasting blood and second morning void urine samples from 93 NIDDM patients and 33 healthy volunteers. Significant differences in chromium homeostasis were seen between patients and controls. NIDDM patients had mean levels of plasma chromium around 33% lower and urine values almost 100% higher than those found in health. Healthy volunteers showed a significant negative correlation between fasting levels of plasma chromium and insulin. This was not evident in NIDDM patients. In the early years of onset of NIDDM, plasma chromium values were inversely correlated with plasma glucose. This was lost in patients with diabetes of more than 2 years duration. We suggest large losses of chromium over many years may exacerbate an already compromised chromium status in NIDDM patients and might contribute to the developing insulin resistance seen in patients with type 2 diabetes.

Chromium-7

Am J Clin Nutr. 1991 Nov;54(5):909-16.

[Related Articles, Links](#)

Supplemental-chromium effects on glucose, insulin, glucagon, and urinary chromium losses in subjects consuming controlled low-chromium diets.

Anderson RA, Polansky MM, Bryden NA, Canary JJ.

Vitamin and Mineral Nutrition Laboratory, US Department of Agriculture, Beltsville, MD 20705.

The effects of low-chromium diets containing chromium in the lowest quartile of normal intake on glucose tolerance and related variables in 11 females and 6 male subjects were evaluated. Subjects with glucose concentration greater than 5.56 mmol/L but less than 11.1 mmol/L 90 min after an oral-glucose challenge were designated as the hyperglycemic group and the remainder, the control group. Glucose tolerance and circulating insulin and glucagon of the hyperglycemic group all improved during chromium supplementation (200 micrograms/d) whereas those of the control group were unchanged. Glucose and insulin concentrations 60 min after the oral-glucose challenge and the sum of the 0-90 min and 0-240 min glucose values were all significantly

lower after chromium supplementation in the hyperglycemic group. These data demonstrate that consumption of diets in the lowest 25% of normal chromium intake lead to detrimental effects on glucose tolerance, insulin, and glucagon in subjects with mildly impaired glucose tolerance.

Chromium-8

Toxicology. 2002 Oct 30;180(1):5-22.

[Related Articles, Links](#)

Cytotoxicity and oxidative mechanisms of different forms of chromium.

Bagchi D, Stohs SJ, Downs BW, Bagchi M, Preuss HG.

Chromium exists mostly in two valence states in nature: hexavalent chromium [chromium(VI)] and trivalent chromium [chromium(III)]. Chromium(VI) is commonly used in industrial chrome plating, welding, painting, metal finishes, steel manufacturing, alloy, cast iron and wood treatment, and is a proven toxin, mutagen and carcinogen. The mechanistic cytotoxicity of chromium(VI) is not completely understood, however, a large number of studies demonstrated that chromium(VI) induces oxidative stress, DNA damage, apoptotic cell death and altered gene expression. Conversely, chromium(III) is essential for proper insulin function and is required for normal protein, fat and carbohydrate metabolism, and is acknowledged as a dietary supplement. In this paper, comparative concentration- and time-dependent effects of chromium(VI) and chromium(III) were demonstrated on increased production of reactive oxygen species (ROS) and lipid peroxidation, enhanced excretion of urinary lipid metabolites, DNA fragmentation and apoptotic cell death in both in vitro and in vivo models. Chromium(VI) demonstrated significantly higher toxicity as compared with chromium(III). To evaluate the role of p53 gene, the dose-dependent effects of chromium(VI) were assessed in female C57BL/6Ntac and p53-deficient C57BL/6TSG p53 mice on enhanced production of ROS, lipid peroxidation and DNA fragmentation in hepatic and brain tissues. Chromium(VI) induced more pronounced oxidative damage in multiple target organs in p53 deficient mice. Comparative studies of chromium(III) picolinate and niacin-bound chromium(III), two popular dietary supplements, reveal that chromium(III) picolinate produces significantly more oxidative stress and DNA damage. Studies have implicated the toxicity of chromium picolinate in renal impairment, skin blisters and pustules, anemia, hemolysis, tissue edema, liver dysfunction; neuronal cell injury, impaired cognitive, perceptual and motor activity; enhanced production of hydroxyl radicals, chromosomal aberration, depletion of antioxidant enzymes, and DNA damage. Recently, chromium picolinate has been shown to be mutagenic and picolinic acid moiety appears to be responsible as studies show that picolinic acid alone is clastogenic. Niacin-bound chromium(III) has been demonstrated to be more bioavailable and efficacious and no toxicity has been reported. In summary, these studies demonstrate that a cascade of cellular events including oxidative stress, genomic DNA damage and modulation of apoptotic regulatory gene p53 are involved in chromium(VI)-induced toxicity and carcinogenesis. The safety of chromium(III) is largely dependent on the ligand, and adequate clinical studies are warranted to demonstrate the safety and efficacy of chromium(III) for human consumption.

Chromium-10

Am J Clin Nutr. 1982 Dec;36(6):1184-93.

[Related Articles, Links](#)

Urinary chromium excretion of human subjects: effects of chromium supplementation and glucose loading.

Anderson RA, Polansky MM, Bryden NA, Roginski EE, Patterson KY, Veillon C, Glinsmann W.

The utilization of inorganic chromium by free-living human subjects was studied in 76 volunteers (male, 48; female, 28) who were supplemented with 200 micrograms of inorganic chromium as chromic chloride or a placebo tablet for 3 months in a double-blind, cross-over experiment. For all subjects, initial mean +/- SEM urinary chromium (Cr) level was 0.20 +/- 0.01 (range, 0.05 to 0.58) ng/ml and did not differ by sex. Initial chromium/creatinine ratio (Cr/Ct) was 0.15 +/- 0.01 (range 0.03 to 0.36) ng Cr/mg creatinine for females and

was significantly lower, 0.10 +/- 0.01 (range 0.03 to 0.36) for males. Mean urinary Cr level increased to 1.0 +/- 0.12 after 2 and to 1.13 +/- 0.08 ng/ml after 3 months' supplementation. The Cr/Ct ratio increased to 0.69 +/- 0.10 for females and to 0.50 +/- 0.04 for males after 2 months' supplementation; values were similar after 3 months. An increase in urinary Cr excretion in response to a glucose load was demonstrated for nonsupplemented normal free-living subjects but not for subjects supplemented daily with trivalent chromium. Urinary Cr excretion after a glucose challenge was not predictable and did not depend on Cr status.

Copper-1

Pol Arch Med Wewn. 1995 Sep;94(3):228-34.

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Activity of superoxide dismutase in erythrocytes and leukocytes and levels of zinc and copper in blood of patients with diabetes. Effect of diabetic treatment on examined parameters **Zbronska H, Grzeszczak W, Jendryczko A, Zbronski R, Kuzniewicz R.**

Katedra i Klinika Chorob Wewnętrznych i Zawodowych w Zabrze.

The purpose of the present work was to assess the relationship of leukocyte and erythrocyte superoxide dismutase activity to its cofactors concentrations i.e. zinc and copper in plasma and erythrocyte in diabetic patients and treatment variability. 104 patients were included in the study. 23 persons were in the control group. All patients were divided into 2 groups (NIDDM and IDDM). Patients with NIDDM were divided into 3 subgroups depending on treatment (insulin, gliclazide, dietary treated). In all groups, there were assessed following parameters: the leukocyte and erythrocyte SOD activity according to the method of Misra and Fridovich, and zinc and copper concentrations in plasma and erythrocyte, which were measured by flame absorption spectrophotometry. Statistical analysis was performed using the CRISP program. **CONCLUSION: 1. The leukocyte and erythrocyte superoxide dismutase activity is significantly lowered in diabetes mellitus. 2. In diabetic patients both in type I and type II as in the healthy people, there is a close correlation between SOD activity and its cofactors i.e. zinc and copper erythrocyte concentrations. 3. Insulin and gliclazide treatment increases SOD activity and delays late diabetic complications.**

Coenzyme Q10-1

 ELSEVIER
FULL-TEXT ARTICLE

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

Folate1

Diabetologia. 2002 Jul;45(7):1004-10. Epub 2002 Jun 06.

[Related Articles, Links](#)

 SpringerLink
FULL-TEXT ARTICLE

Impaired NO-dependent vasodilation in patients with Type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate.

van Etten RW, de Koning EJ, Verhaar MC, Gaillard CA, Rabelink TJ.

Department of Vascular Medicine and Diabetes, University Medical Center, Utrecht, The Netherlands.

AIMS/HYPOTHESIS: Patients with diabetes are characterised by endothelial dysfunction and cardiovascular mortality. In particular endothelium-derived nitric oxide has emerged as a first line mechanism against atherosclerosis. Hyperglycaemia causes oxygen radical stress but has also been associated with endothelial nitric oxide synthase uncoupling, both lead to decreased nitric oxide-availability. We recently showed that folate reverses eNOS uncoupling in vitro. Therefore we hypothesise that folate improves endothelial function in Type II (non-insulin-dependent) diabetes mellitus in vivo. **METHODS:** Using forearm plethysmography, we evaluated the effect of local, intra-arterial administration of 5-methyltetrahydrofolate (5-MTHF, the active form of folic acid, 1 microg/100 ml FAV/min) on forearm blood flow in 23 patients with Type II diabetes and 21 control subjects, matched for age, sex, blood pressure, body mass index, weight and smoking habits. Serotonin as a stimulator of nitric oxide-dependent vasodilation and sodium nitroprusside as a stimulator of endothelium-independent vasodilation were infused. **RESULTS:** Serotonin-induced vasodilation was blunted (53+/-30 vs 102+/-66 M/C%, $p < 0.005$) and nitroprusside-induced vasodilation was mildly reduced (275+/-146 vs 391+/-203 M/C%, $p < 0.05$) in patients with Type II diabetes compared to control subjects. 5-MTHF improved nitric oxide-mediated vasodilation (from 53+/-30 to 88+/-59 M/C%, $p < 0.05$) in patients with Type II diabetes mellitus. As expected, 5-MTHF had no effect on forearm blood flow in control subjects.

CONCLUSION/INTERPRETATION: These data imply that folate can be used to improve nitric oxide status and to restore endothelial dysfunction in patients with Type II diabetes. Our results provide a strong rationale for the initiation of studies that investigate whether supplementation with folic acid prevents future cardiovascular events in this patient group.

Folate 2

Diabetes. 2002 Jul;51(7):2282-6.

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diabetes.
diabetesjournals.org

Endothelial dysfunction relates to folate status in children and adolescents with type 1 diabetes.

Wiltshire EJ, Gent R, Hirte C, Pena A, Thomas DW, Couper JJ.

Department of Paediatrics, Wellington School of Medicine and Health Sciences, PO Box 7343, Wellington South, New Zealand. esko@winmeds.ac.nz

Endothelial dysfunction occurs early in the development of vascular disease in diabetes. Total plasma homocyst(e)ine (tHcy) is associated with endothelial dysfunction. We therefore aimed to assess endothelial function in children with type 1 diabetes in relation to tHcy and its determinants. Endothelial function was assessed in 36 children with type 1 diabetes aged 13.7 +/- 2.2 years and 20 age- and sex-matched control subjects using ultrasound assessment of flow-mediated dilatation (FMD) and glyceryl trinitrate (GTN)-dependent brachial artery responses. von Willebrand factor (vWF) and thrombomodulin, markers of endothelial activation, were measured in 64 children with type 1 diabetes and 52 control subjects. Fasting glucose, tHcy, serum and red cell folate, vitamin B12, HbA(1c), creatinine, and lipids were also measured. FMD (5.2 +/- 4.7 vs. 9.1 +/- 4.0%, $P = 0.002$) and the ratio of FMD:GTN-induced dilatation (0.22 +/- 0.39 vs. 0.41 +/- 0.29%, $P = 0.008$) were significantly lower in diabetic subjects, indicating endothelial dysfunction. In diabetic subjects, red cell folate correlated independently with FMD (beta = 0.42, $P = 0.028$) and the ratio of FMD:GTN-induced dilatation (beta = 0.59, $P < 0.001$). Resting vessel diameter correlated independently with tHcy (beta = -0.51, $P < 0.001$) and height (beta = 0.65, $P < 0.001$). vWF correlated independently with HbA(1c) (beta = 0.38, $P = 0.003$), and thrombomodulin correlated independently with red cell folate (beta = -0.38, $P = 0.005$), tHcy (beta

= -0.37, $P = 0.004$), diastolic blood pressure ($\beta = -0.28$, $P = 0.025$), and creatinine clearance ($\beta = 0.26$, $P = 0.033$). Children with type 1 diabetes have early endothelial dysfunction. Better folate status is associated with better endothelial function, as measured by higher FMD, higher FMD:GTN ratio, and lower thrombomodulin. Folate may therefore protect against endothelial dysfunction in children with diabetes.

Folate 3

Am J Hypertens. 1998 Sep;11(9):1100-7.

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Plasma homocysteine and folate are related to arterial blood pressure in type 2 diabetes mellitus.

Fiorina P, Lanfredini M, Montanari A, Peca MG, Veronelli A, Mello A, Astorri E, Craveri A.

Divisione di Medicina II, Ospedale San Paolo, Milano, Italy.

The aim of this study was to assess the relationship between homocysteine (tHcy), folate and vitamin B12 levels, urinary albumin excretion, and arterial blood pressure in patients with non-insulin-dependent diabetes mellitus (NIDDM). Our study was carried out in 33 NIDDM patients (16 men, 17 women) and 16 healthy volunteers as controls (seven men, nine women). Fasting and postmethionine load plasma tHcy levels were assessed, together with folate, vitamin B12, and urinary albumin excretion levels. In NIDDM patients, there were correlations between folate and mean arterial pressure ($r = -0.352$, $P = .046$), folate and systolic blood pressure ($r = -0.437$, $P = .013$), folate and vitamin B12 ($r = 0.499$, $P = .004$), tHcy and vitamin B12 ($r = -0.348$, $P = .04$), ln tHcy and ln folate ($r = -0.404$, $P = .01$), and, lastly, between tHcy, either fasting or postload, and urinary albumin excretion. Patients with elevated tHcy levels had significantly higher diastolic blood pressure ($P = .04$) and mean arterial pressure ($P = .03$). Otherwise, higher folate values were associated with lower systolic blood pressure ($P = .004$) and mean arterial pressure ($P = .02$). In addition, NIDDM patients with complications presented higher tHcy basal values than the group without complications ($P = .003$). A particular propensity of such patients towards endothelial dysfunction could explain the presence of correlations between these metabolic parameters and arterial blood pressure.

Green Tea-1

J Agric Food Chem. 2000 Nov; 48(11): 5618-23.

[Related Articles, Links](#)



Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism.

Kobayashi Y, Suzuki M, Satsu H, Arai S, Hara Y, Suzuki K, Miyamoto Y, Shimizu M.

Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan.

Intestinal glucose uptake is mainly performed by the sodium-dependent glucose transporter, SGLT1. The transport activity of SGLT1 was markedly inhibited by green tea polyphenols, this inhibitory activity being most pronounced in polyphenols having galloyl residues such as epicatechin gallate (ECg) and epigallocatechin gallate (EGCg). Experiments using brush-border membrane vesicles obtained from the rabbit small intestine demonstrated that ECg inhibited SGLT1 in a competitive manner, although ECg itself was not transported via SGLT1. The present results suggest that tea polyphenols such as ECg interact with SGLT1 as antagonist-like molecules, possibly playing a role in controlling the dietary glucose uptake in the intestinal tract.

Inositol-1

Int J Exp Diabetes Res. 2002;3(1):47-60.

[Related Articles, Links](#)

D-chiro-inositol--its functional role in insulin action and its deficit in insulin resistance.

Larner J.

In this review we discuss the biological significance of D-chiro-inositol, originally discovered as a component of a putative mediator of intracellular insulin action, where as a putative mediator, it accelerates the dephosphorylation of glycogen synthase and pyruvate dehydrogenase, rate limiting enzymes of non-oxidative and oxidative glucose disposal. Early studies demonstrated a linear relationship between its decreased urinary excretion and the degree of insulin resistance present. When tissue contents, including muscle, of type 2 diabetic subjects were assayed, they demonstrated a more general body deficiency. Administration of D-chiro-inositol to diabetic rats, Rhesus monkeys and now to humans accelerated glucose disposal and sensitized insulin action. A defect in vivo in the epimerization of myo-inositol to chiro-inositol in insulin sensitive tissues of the GK type 2 diabetic rat has been elucidated. Thus, administered D-chiro-inositol may act to bypass a defective normal epimerization of myo-inositol to D-chiro-inositol associated with insulin resistance and act to at least partially restore insulin sensitivity and glucose disposal.

Inositol -2

Endocrinology. 1993 Feb;132(2):646-51.

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Chiroinositol deficiency and insulin resistance. II. Acute effects of D-chiroinositol administration in streptozotocin-diabetic rats, normal rats given a glucose load, and spontaneously insulin-resistant rhesus monkeys.

Ortmeyer HK, Huang LC, Zhang L, Hansen BC, Larner J.

The acute effects of administration of D-chiroinositol (D-CI), a component of a putative mediator of insulin action, on plasma glucose were examined in low dose streptozotocin-treated rats and normal rats given a glucose load and the effects on plasma glucose and insulin were determined in five obese rhesus monkeys with varying degrees of spontaneous insulin resistance. Single dose intragastric D-CI (10 mg/kg) administered to streptozotocin-treated rats produced a 30-40% decrease in plasma glucose ($P < 0.05$) at 30-120 min. Single dose intragastric D-CI (2-15 mg/kg) administered to normal rats 2 h before ip glucose produced a 30-50% decrease ($P < 0.05$) in plasma glucose. D-CI (10 mg/kg) caused a 50% increase ($P < 0.05$) in glucose disappearance rates in these rats. Myo-inositol (10 mg/kg) was without effect. Intravenously administered single dose D-CI (100 mg/kg) increased both the glucose and insulin disappearance rates by $129 \pm 41\%$ (mean \pm SE; $P < 0.06$) and $89 \pm 39\%$ ($P = 0.01$), respectively, in all monkeys between 0-30 min compared to control values. D-CI administration, therefore, lowered elevated plasma glucose in streptozotocin-treated hyperglycemic rats, normal rats given a glucose load, and spontaneously insulin-resistant monkeys with or without noninsulin-dependent diabetes mellitus. Intravenous D-CI also lowered plasma insulin in these monkeys.

Inositol -3

Endocrinology. 1993 Feb;132(2):640-5.

[Related Articles, Links](#)

Chiroinositol deficiency and insulin resistance. I. Urinary excretion rate of chiroinositol is directly associated with insulin resistance in spontaneously diabetic rhesus monkeys.

Ortmeyer HK, Bodkin NL, Lilley K, Larner J, Hansen BC.

Previously, we demonstrated that nondiabetic insulin-resistant monkeys had reduced covalent insulin activation of muscle glycogen synthase (GS) compared to normal monkeys and that covalent insulin activation of adipose tissue GS was absent in these monkeys. Covalent insulin activation of muscle and adipose tissue GS in monkeys

with impaired glucose tolerance and noninsulin-dependent diabetes (NIDDM) was also absent. As in humans, monkeys with NIDDM have a lower urinary excretion rate of chiroinositol (CI), a component of a putative mediator of insulin action, compared to normal monkeys. To determine whether the urinary excretion rate of CI was related to insulin resistance, which develops naturally in many obese rhesus monkeys, we examined the relationships between 24-h urinary CI excretion rate and 1) whole body insulin-mediated glucose disposal rates (M) and insulin-mediated changes in 2) the skeletal muscle GS activity ratio (sm delta GSAR), 3) the skeletal muscle glycogen phosphorylase activity ratio, and 4) the adipose tissue GS activity ratio (at delta GSAR) in 27 monkeys ranging from normal (n = 12) to insulin resistant (n = 8) to overtly diabetic (n = 7). The urinary CI excretion rate was significantly correlated with M ($r = 0.47$; $P < 0.02$), sm delta GSAR ($r = 0.38$; $P < 0.05$), skeletal muscle glycogen phosphorylase activity ratio ($r = -0.49$; $P < 0.01$), and at delta GSAR ($r = 0.46$; $P < 0.02$). The urinary CI excretion rate was also correlated with glucose tolerance ($r = 0.39$; $P < 0.05$). There was a wide range of urinary CI excretion rates (0.42-5.17 $\mu\text{mol/day}$) in monkeys with normal fasting plasma glucose concentrations. However, of the 7 diabetic monkeys, 6 had a urinary CI excretion rate below 2.0 $\mu\text{mol/day}$, and in the subgroup of 16 monkeys with a urinary CI excretion rate less than 2.0 $\mu\text{mol/day}$, the associations of urinary CI with M rate ($r = 0.65$; $P < 0.005$), glucose tolerance ($r = 0.63$; $P < 0.01$), and sm delta GSAR ($r = 0.73$; $P < 0.001$) increased in strength and significance. We propose that the urinary CI excretion rate may be 1) a biochemical indicator of both in vivo and in vitro insulin resistance and 2) a noninvasive diagnostic tool with potential for the identification of those individuals at risk for NIDDM and other related diseases with insulin resistance.

Inositol -4

Int J Exp Diabetes Res. 2002;3(1):47-60.

[Related Articles, Links](#)

D-chiro-inositol--its functional role in insulin action and its deficit in insulin resistance.

Larner J.

In this review we discuss the biological significance of D-chiro-inositol, originally discovered as a component of a putative mediator of intracellular insulin action, where as a putative mediator, it accelerates the dephosphorylation of glycogen synthase and pyruvate dehydrogenase, rate limiting enzymes of non-oxidative and oxidative glucose disposal. Early studies demonstrated a linear relationship between its decreased urinary excretion and the degree of insulin resistance present. When tissue contents, including muscle, of type 2 diabetic subjects were assayed, they demonstrated a more general body deficiency. Administration of D-chiro-inositol to diabetic rats, Rhesus monkeys and now to humans accelerated glucose disposal and sensitized insulin action. A defect in vivo in the epimerization of myo-inositol to chiro-inositol in insulin sensitive tissues of the GK type 2 diabetic rat has been elucidated. Thus, administered D-chiro-inositol may act to bypass a defective normal epimerization of myo-inositol to D-chiro-inositol associated with insulin resistance and act to at least partially restore insulin sensitivity and glucose disposal.

Inositol -5

Proc Natl Acad Sci U S A. 1993 Nov 1;90(21):9988-92.

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D-chiro-inositol metabolism in diabetes mellitus.

Ostlund RE Jr, McGill JB, Herskowitz I, Kipnis DM, Santiago JV, Sherman WR.

D-chiro-inositol is a rare inositol isomer present in inositol phosphoglycans which are proposed mediators of insulin action. To study D-chiro-inositol metabolism in diabetes mellitus, a sensitive and specific assay was developed using negative-ion chemical ionization gas chromatography/mass spectrometry. Median urinary D-chiro-inositol excretion, which was 2.1 $\mu\text{mol/day}$ in nondiabetics, was substantially increased to 12 $\mu\text{mol/day}$ in non-insulin-dependent diabetes ($P < 0.0001$) and to 74 $\mu\text{mol/day}$ in insulin-dependent diabetes

($P < 0.0001$). Urinary D-chiro-inositol was strongly correlated with fasting plasma glucose ($r = 0.568$, $P < 0.0001$), glycated hemoglobin ($r = 0.529$, $P < 0.0001$), and urinary glucose ($r = 0.368$, $P = 0.01$). The renal clearance of D-chiro-inositol was selectively elevated in both non-insulin-dependent and insulin-dependent diabetes when compared with the clearances of L-chiro-inositol or myo-inositol and exceeded the glomerular filtration rate in 71% of the diabetics but in none of the nondiabetics. In poorly controlled diabetic patients insulin treatment reduced urinary D-chiro-inositol losses by 63% and increased plasma levels by 8.8-fold. The metabolism of D-chiro-inositol is abnormal in diabetes and appears to be influenced by short- and long-term metabolic control.

Lipoic-1. Jacob S, Ruus P, Hermann R, **Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial.** *Free Radic Biol Med.* 1999 Aug;27(3-4):309-14.

Alpha-lipoic acid (ALA), a naturally occurring compound and a radical scavenger was shown to enhance glucose transport and utilization in different experimental and animal models. Clinical studies described an increase of insulin sensitivity after acute and short-term (10 d) parenteral administration of ALA. The effects of a 4-week oral treatment with alpha-lipoic acid were evaluated in a placebo-controlled, multicenter pilot study to determine whether oral treatment also improves insulin sensitivity. Seventy-four patients with type-2 diabetes were randomized to either placebo ($n = 19$); or active treatment in various doses of 600 mg once daily ($n = 19$), twice daily (1200 mg; $n = 18$), or thrice daily (1800 mg; $n = 18$) alpha-lipoic acid. An isoglycemic glucose-clamp was done on days 0 (pre) and 29 (post). In this explorative study, analysis was done according to the number of subjects showing an improvement of insulin sensitivity after treatment. Furthermore, the effects of active vs. placebo treatment on insulin sensitivity was compared. All four groups were comparable and had a similar degree of hyperglycemia and insulin sensitivity at baseline. When compared to placebo, significantly more subjects had an increase in insulin-stimulated glucose disposal (MCR) after ALA treatment in each group. As there was no dose effect seen in the three different alpha-lipoic acid groups, all subjects receiving ALA were combined in the "active" group and then compared to placebo. This revealed significantly different changes in MCR after treatment (+27% vs. placebo; $p < .01$). This placebo-controlled explorative study confirms previous observations of an increase of insulin sensitivity in type-2 diabetes after acute and chronic intravenous administration of ALA. The results suggest that oral administration of alpha-lipoic acid can improve insulin sensitivity in patients with type-2 diabetes. The encouraging findings of this pilot trial need to be substantiated by further investigations.

Lipoic-2.

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Konrad T, Vicini P, **Alpha-Lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes.** *Diabetes Care.* 1999 Feb;22(2):280-7.

OBJECTIVE: We examined the effect of lipoic acid (LA), a cofactor of the pyruvate dehydrogenase complex (PDH), on insulin sensitivity (SI) and glucose effectiveness (SG) and on serum lactate and pyruvate levels after oral glucose tolerance tests (OGTTs) and modified frequently sampled intravenous glucose tolerance tests (FSIGTTs) in lean ($n = 10$) and obese ($n = 10$) patients with type 2 diabetes. **RESEARCH DESIGN AND METHODS:** FSIGTT data were analyzed by minimal modeling technique to determine SI and SG before and after oral treatment (600 mg, twice a day, for 4 weeks). Serum lactate and pyruvate levels of diabetic patients after glucose loading were compared with those of lean ($n = 10$) and obese ($n = 10$) healthy control subjects in which SI and SG were also determined from FSIGTT data. **RESULTS:** Fasting lactate and pyruvate levels were significantly increased in patients with type 2 diabetes. These metabolites did not exceed elevated fasting concentrations after glucose loading in lean patients with type 2 diabetes. However, a twofold increase of lactate and pyruvate levels was measured in obese diabetic patients. LA treatment was associated with increased SG in both diabetic groups (lean 1.28 ± 0.14 to 1.93 ± 0.13 ; obese 1.07 ± 0.11 to $1.53 \pm 0.08 \times 10^{-2} \text{ min}^{-1}$, $P < 0.05$). Higher SI and lower fasting glucose were measured in lean diabetic patients only ($P < 0.05$). Lactate and

pyruvate before and after glucose loading were approximately 45% lower in lean and obese diabetic patients after LA treatment. CONCLUSIONS: Treatment of lean and obese diabetic patients with LA prevents hyperglycemia-induced increments of serum lactate and pyruvate levels and increases SG.

Lipoic-3

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Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care. 1999 Aug;22(8):1296-301.

OBJECTIVE: To evaluate the efficacy and safety of alpha-lipoic acid given intravenously, followed by oral treatment in type 2 diabetic patients with symptomatic polyneuropathy. **RESEARCH DESIGN AND METHODS:** In a multicenter randomized double-blind placebo-controlled trial (Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN] III Study), 509 outpatients were randomly assigned to sequential treatment with 600 mg alpha-lipoic acid once daily intravenously for 3 weeks, followed by 600 mg alpha-lipoic acid three times a day orally for 6 months (A-A; n = 167); 600 mg alpha-lipoic acid once daily intravenously for 3 weeks, followed by placebo three times a day orally for 6 months (A-P; n = 174); and placebo once daily intravenously for 3 weeks, followed by placebo three times a day orally for 6 months (P-P; n = 168). Outcome measures included the Total Symptom Score (TSS) for neuropathic symptoms (pain, burning, paresthesias, and numbness) in the feet, and the Neuropathy Impairment Score (NIS). Data analysis was based on the intention to treat. **RESULTS:** No significant differences between the groups were noted for the demographic variables and the nerve function parameters at baseline. The TSS in the feet decreased from baseline to day 19 (median [range]) by -3.7 (-12.6 to 5.0) points in the group given alpha-lipoic acid intravenously and by -3.0 (-12.3 to 8.0) points in the placebo group (P = 0.447), but the area under curve on a daily basis was significantly smaller in the active as compared with the placebo group (85.6 [0-219] vs. 95.9 [5.5-220]); P = 0.033). After 7 months, the changes in the TSS from baseline were not significantly different between the three groups studied, which could be due to increasing intercenter variability in the TSS during the trial. The NIS decreased after 19 days by -4.34±0.35 points (mean ± SEM) in A-A and A-P and -3.49±0.58 points in P-P (P = 0.02 for alpha-lipoic acid versus placebo) and after 7 months by -5.82±0.73 points in A-A, -5.76±0.69 points in A-P, and -4.37±0.83 points in P-P (P = 0.09 for A-A vs. P-P). The rates of adverse events were not different between the groups throughout the study. **CONCLUSIONS:** These findings indicate that a 3-week intravenous treatment with alpha-lipoic acid, followed by a 6-month oral treatment, was associated with a favorable effect on neuropathic deficits without causing significant adverse reactions. Long-term trials that focus on neuropathic deficits rather than symptoms as the primary criterion of efficacy are needed to see whether oral treatment with alpha-lipoic acid over several years may slow or reverse the progression of diabetic neuropathy.

Lipoic-4

ELSEVIER
FULL-TEXT ARTICLE

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

Manganese 1

Baly DL, Schneiderman JS. Effect of manganese deficiency on insulin binding, glucose transport and metabolism in rat adipocytes. J Nutr. 1990 Sep;120(9):1075-9.

The effect of manganese deficiency on insulin binding, glucose transport and metabolism in isolated adipose cells from Sprague-Dawley rats was investigated. Offspring from Mn-sufficient female rats fed 45 micrograms Mn/g diet (control) and from Mn-deficient (Mn-) female rats fed 1 microgram Mn/g diet were used in these studies. Both basal and insulin-stimulated 3-O-methylglucose transport in isolated adipose cells was significantly lower in Mn- rats, averaging 40% and 50% of control values, respectively. Kinetic analysis of glucose transport demonstrated a lower maximal transport velocity (V_{max}) for glucose in adipose cells from Mn- rats compared to controls. No differences in the K_m for glucose uptake were observed between the two groups. Insulin-stimulated glucose oxidation to CO₂ and conversion to triglycerides was lower in isolated adipose cells from Mn- rats compared to controls. Mn- animals had fewer insulin receptors per cell compared to controls, although no differences in insulin receptor affinity were observed between the two groups. These data suggest that **Mn deficiency affects glucose transport and metabolism in the adipose cell. The apparent defect lies distal to the insulin receptor and probably reflects a decreased number of glucose transporters in adipose tissue** of Mn- rats.

Manganese 2

Baly DL, Curry DL. Dynamics of insulin and glucagon release in rats: influence of dietary manganese. Endocrinology. 1985 May;116(5):1734-40.

The effect of manganese on endocrine pancreatic function was examined in manganese-sufficient (control) and manganese-deficient (Mn-) Sprague-Dawley rats. Pancreatic insulin release was lower (P less than 0.05) in Mn- rats than in controls in response to both a 300 mg/dl and a 100 mg/dl glucose stimulus. The 300 mg/dl glucose stimulus induced the synthesis of 19.4 micrograms insulin/g pancreas in control rats. Additionally, no appreciable intracellular degradation of insulin occurred over an 80-min perfusion period. By contrast, in Mn- rats, there occurred an intracellular insulin degradation amounting to 7.8 micrograms/g pancreas. This enhanced degradation was partially compensated by a net insulin synthesis of only 3.4 micrograms insulin/g pancreas. Initial (min 1-3) insulin release by Mn- rats in response to 10 mM arginine was lower (P less than 0.05) than that observed in controls. Pancreatic glucagon release in response to 10 mM arginine was not affected by manganese deficiency. These findings demonstrate **that manganese deficiency results in depressed pancreatic insulin synthesis and enhanced degradation. These factors may be responsible for the abnormal carbohydrate metabolism observed in Mn- animals.**

Niacinamide-1



K1.Hoorens A, Pipeleers D. Nicotinamide protects human beta cells against chemically-induced necrosis, but not against cytokine-induced apoptosis. Diabetologia. 1999 Jan;42(1):55-9.

Nicotinamide intervention trials are presently undertaken to prevent Type I (insulin-dependent) diabetes in high risk subjects. They are based on studies in rodents reporting nicotinamide protection against beta-cell injury in

vitro and in vivo. This study examines whether nicotinamide can protect human beta cells in vitro. At concentrations (2 and 5 mmol/l) to protect rat beta cells against necrosis by streptozotocin or hydrogen peroxide, nicotinamide prevents hydrogen peroxide-induced necrosis of human beta cells. As with rat beta cells, nicotinamide fails to protect human beta cells against apoptosis induced by a combination of the cytokines interleukin-1beta, interferon-gamma and tumour necrosis factor-alpha. In rat beta cells, nicotinamide (2 to 20 mmol/l) was also found to induce apoptosis, in particular during the days following its protection against necrosis; this cytotoxic effect was not observed with human beta cells. These data demonstrate that **nicotinamide can protect human beta cells against radical-induced necrosis**, but not against cytokine-induced apoptosis. This effect is not associated with a delayed apoptosis as in rat beta cells.

Niacinamide-2

K2. Polo V, Saibene A, Pontiroli AE. Nicotinamide improves insulin secretion and metabolic control in lean type 2 diabetic patients with secondary failure to sulphonylureas. Acta Diabetol. 1998 Apr;35(1):61-4.

Eighteen patients with non-insulin-dependent (type 2) diabetes mellitus of normal body weight [body mass index (BMI) <25 kg/m²] without signs of autoimmunity [negative for islet cell antibodies (ICA)], with secondary failure of sulphonylureas, defined as persistent hyperglycaemia in spite of maximal doses of sulphonylureas, were evaluated for C-peptide release under basal conditions and 6 min after i.v. glucagon, for glycosylated haemoglobin (HbA1C), and for fasting and mean daily blood glucose levels. They entered a 6-month, single-blind study in which they were randomly assigned to one of three treatments: (1) insulin plus nicotinamide (group 1, 0.5 g, three tablets/day); (2) insulin plus placebo (group 2, 3 tablets/day); (3) current sulphonylureas plus nicotinamide (group 3, 0.5 g, three tablets/day). They were re-evaluated for C-peptide, HbA1C, and fasting and mean daily blood glucose levels after 6 months. Compared with group 2, C-peptide release increased in both groups 1 and 3, while HbA1C, fasting and mean daily blood glucose levels improved in the three groups to the same extent. With multiple regression analysis, nicotinamide administration was the only significant factor for the improvement of C-peptide release. These data indicate that **nicotinamide improves C-peptide release in type 2 diabetic patients with secondary failure of sulphonylureas, leading to a metabolic control similar to patients treated with insulin.**

Niacinamide-3

K3. Kolb H, Burkart V. Nicotinamide in type 1 diabetes. Mechanism of action revisited. Diabetes Care. 1999 Mar;22 Suppl 2:B16-20.

Treatment with high doses of nicotinamide (niacinamide, vitamin B3) prevents or delays insulin-deficient diabetes in several animal models of type 1 diabetes and protects islet cells against cytotoxic actions in vitro. In recent-onset type 1 diabetes, nicotinamide administration improves beta-cell function, without significantly decreased insulin requirements. This review discusses the possible mechanism of action of nicotinamide in vivo. It is proposed that the key target of nicotinamide is the poly(ADP-ribose)polymerase (PARP), and to a lesser extent (mono)ADP-ribosyl transferases (ADPRTs). Suppression of PARP activity by nicotinamide not only decreases consumption of NAD⁺, the substrate of PARP, but also has major regulatory effects on gene expression, as shown for the major histocompatibility complex class II gene. In addition, PARP activity controls early steps of apoptosis. The possible suppression of ADPRTs by nicotinamide would also affect CD38, a membrane-bound external ADP-ribosyl transferase with potent immunoregulatory properties. Taken together, it is proposed that high doses of nicotinamide primarily affect ADP-ribosylation reactions in beta-cells as well as in immune cells and the endothelium. As a consequence, **cell death pathways and gene expression patterns are modified, leading to improved beta-cell survival and an altered immunoregulatory balance.**

Omega-3 fats-1

J Nutr. 1996 Aug;126(8):1951-8.

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Dietary (n-3) polyunsaturated fatty acids improve adipocyte insulin action and glucose

metabolism in insulin-resistant rats: relation to membrane fatty acids.

Luo J, Rizkalla SW, Boillot J, Alamowitch C, Chaib H, Bruzzo F, Desplanque N, Dalix AM, Durand G, Slama G.

To study the effects of dietary fish oil on insulin-stimulated glucose metabolism in adipocytes of insulin-resistant rats (rats fed 50% sucrose and 30% fat), eighteen 5-wk-old Sprague-Dawley rats were fed, for 6 wk, a diet containing 30% fat as either fish oil (FO) or a mixture of vegetable and animal oils [control oils (CO)]. A third reference group was fed a standard diet (62% corn starch and 13% fat). At the end of the 6-wk period, the two experimental groups had comparable plasma glucose concentrations that were higher than that found in the reference group. FO feeding corrected the hyperinsulinemia of the experimental rats ($P < 0.05$) to reach values in the reference group. Plasma triacylglycerol ($P < 0.01$) and cholesterol ($P < 0.001$) concentrations were also lower in rats fed FO than in those fed CO. The body weights of FO-fed rats were similar to that of CO-fed rats, but epididymal adipose tissue weight was lower ($P < 0.01$). Adipocytes of FO-fed rats, compared with those of CO-fed rats, had high insulin-stimulated glucose transport ($P < 0.05$), oxidation ($P < 0.001$) and incorporation into total lipids ($P < 0.05$). The incorporation of (n-3) polyunsaturated fatty acids in adipocyte membrane phospholipids was higher in FO-fed rats than in those fed CO ($P < 0.0001$). Insulin action was positively correlated with the fatty acid unsaturation index in membrane phospholipids. Thus dietary fish oil has beneficial effects on insulinemia, plasma lipids and insulin-stimulated glucose metabolism in insulin-resistant slightly diabetic rats.

Omega-3 fats -2

Diabetes Care. 1996 May;19(5):463-7.

[Related Articles, Links](#)

A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes.

McManus RM, Jumpson J, Finegood DT, Clandinin MT, Ryan EA.

Department of Medicine, University of Alberta, Edmonton, Canada.

OBJECTIVE--Supplementation of type II diabetic diets with n-3 fatty acids (FAs) from fish oil (FO) has been associated with lowered triglyceride and VLDL levels, although reports of impaired glycemic control have limited their use. Effects of n-3FAs from nonmarine sources are less well documented. Therefore, an investigation comparing the effects of linseed oil (LO) with FO supplementation was undertaken in subjects with type II diabetes. **RESEARCH DESIGN AND METHODS**--Eleven subjects with type II diabetes were given supplements with LO and FO for 3 months each in a randomized double-blind crossover fashion after 3 months of olive oil placebo. Oils were given as 35 mg FA.kg body wt⁻¹.day⁻¹. After each 3-month period, fasting glucose and insulin levels, HbA1c, lipid profiles, insulin sensitivity (SI), glucose effectiveness (SG), and acute insulin response to glucose (AIRG) were evaluated. **RESULTS**--HbA1c and lipid values were within the normal range at randomization. Repeated measures analysis of variance testing found no significant differences in weight; fasting glucose and insulin levels; HbA1c; total, LDL, and HDL cholesterol levels; SI; SG; or AIRG with either active oil. FO was associated with significant reductions in triglycerides and a trend toward decreased SI. **CONCLUSIONS**--In a population with well-controlled type II diabetes, 3 months of FO but not LO resulted in lowered triglyceride levels. Neither LO nor FO significantly affected glycemic control, cholesterol values, SG, or insulin secretion, while a nonsignificant trend toward decreased insulin sensitivity was found with FO.

Omega-3 fats -3

Biomed Pharmacother. 2002 Oct;56(8):397-406.

[Related Articles, Links](#)

N-3 fatty acids and diabetes.

Sirtori CR, Galli C.

Department of Pharmacological Sciences, University of Milano, Milan, Italy. cesare.sirtori@unimi.it

Fatty acids of the omega-3 series (n-3 fatty acids) are a well established dietary component affecting plasma lipids (mainly triglycerides) and also major cardiovascular parameters, such as arrhythmogenesis. In view of their peculiar metabolic handling, it has been suggested that they may reduce glucose tolerance in patients predisposed to diabetes. On the other hand, insulin is required for the endogenous synthesis of the long chain n-3 fatty acids from precursors; the heart may thus be particularly susceptible to their depletion in diabetes. This review examines large population studies, carried out particularly by this research group, evaluating the risk of developing glucose intolerance/clearcut diabetes in large series of patients with predisposing conditions. While diabetes development was in no way accelerated in any of these studies, there was, instead, clear evidence of a significant hypotriglyceridemic activity of the supplements. In long-term treatments, there was also a tendency toward a significant reduction of low density lipoprotein (LDL) cholesterolemia, with positive effects on high density lipoprotein (HDL). These findings fit well with cellular changes indicative of improved glucose handling. Finally, recent data suggest an improvement of heart rate variability by fish intake in coronary patients, that is also exerted by the n-3 fatty acids given as ethyl esters, thus providing further indication for the potential benefit of such treatments in diabetic patients.

Omega-3 fats -4

Diabetes Care. 1991 Dec;14(12):1160-79.

[Related Articles, Links](#)

Biological effects of omega-3 fatty acids in diabetes mellitus.

Malasanos TH, Stacpoole PW.

Fish oils exert important biological effects on several pathways predisposing to atherosclerosis. Epidemiological studies provided the initial evidence that omega-3 fatty acids may be the principal factor in fish oils responsible for these effects and have led to several short-term clinical trials in which fish-oil concentrates have been administered to various populations at risk for coronary heart disease, including patients with diabetes mellitus. omega-3 Fatty acids reduce serum lipids and lipoproteins, impair platelet aggregation, increase cell membrane fluidity, and lower blood pressure in humans. In this review, we highlight these and other potentially antiatherogenic properties of marine lipids in diabetic subjects.

Omega-3 fats -5

Am J Clin Nutr. 1997 Jun;65(6):1874-81.

[Related Articles, Links](#)

N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. Italian Fish Oil Multicenter Study.

Sirtori CR, Paoletti R, Mancini M, Crepaldi G, Manzato E, Rivellese A, Pamparana F, Stragliotto E.

A multicenter, randomized, double-blind, placebo-controlled study evaluated the possible worsening of glycemic control after a moderate daily intake of n-3 fatty acid ethyl esters in patients with hypertriglyceridemia with and without glucose intolerance or diabetes. A total of 935 patients of both sexes in 63 Italian clinical centers were selected; 55% had either impaired glucose tolerance or non-insulin-dependent diabetes mellitus (NIDDM). They received for 2 mo either 1 g n-3 ethyl esters three times a day or a corresponding placebo, followed by 4 mo of either 1 g n-3 ethyl esters twice a day or placebo. In addition to the complete lipid and lipoprotein evaluation, patients with impaired glucose tolerance also underwent an oral-glucose-tolerance test;

in patients with NIDDM, serum insulin and glycated hemoglobin (Hb A1c) concentrations were determined. Plasma triacylglycerol concentrations decreased significantly, up to 21.53% at 6 mo compared with baseline (decreased 15% compared with placebo), with a tendency toward a progressive reduction with time. There was no evidence for a different response in patients with either NIDDM or impaired glucose tolerance. Among NIDDM patients, the triacylglycerol reduction was greater in those with high-density-lipoprotein cholesterol $<$ or $=$ 0.91 mmol/L. There was no alteration in the major glycemic indexes: fasting glucose, Hb A1c, insulinemia, and oral glucose tolerance in patients with impaired glucose tolerance or NIDDM after treatment with n-3 ethyl esters. Treatment with a moderate daily dose of n-3 ethyl esters over a prolonged period of time significantly reduced triacylglycerol concentrations without any worsening of glucose tolerance in patients with hypertriglyceridemia with and without impaired glycemic regulation.

Omega-3 fats -6

Ann Intern Med. 1995 Dec 15;123(12):911-8.

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Full text article at
www.annals.org

Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial.

Toft I, Bonna KH, Ingebretsen OC, Nordoy A, Jenssen T.

OBJECTIVE: To determine whether dietary supplementation with fish oil adversely affects glycemic control in patients with hypertension. **DESIGN:** Randomized, double-blind, placebo-controlled study. **PATIENTS:** 78 persons with untreated hypertension recruited from a population survey. **INTERVENTION:** Participants were randomly assigned to receive eicosapentaenoic and docosahexaenoic acids, 4 g/d, or corn oil placebo, 4 g/d, for 16 weeks. **MEASUREMENTS:** An oral glucose tolerance test; assessments of insulin release, glucose disposal, and insulin sensitivity done using the hyperglycemic clamp technique to keep plasma glucose levels at 10 mmol/L for 180 minutes; assessment of insulin sensitivity done using a euglycemic hyperinsulinemic clamp technique (infusing insulin and glucose to keep plasma glucose levels at 5 mmol/L); assessments of lipid levels and blood pressure. Measurements were done before and after intervention. **RESULTS:** Changes in integrated glucose and insulin response after the oral glucose challenge did not differ between the fish oil and corn oil groups after intervention (-0.6 ± 0.7 compared with -1.0 ± 0.6 mmol/L [$P > 0.3$] for integrated glucose and 143 ± 76 compared with 169 ± 84 pmol/L [$P > 0.3$] for insulin response). Changes in first-phase insulin release (34 ± 72 pmol/L in the fish oil group compared with 191 ± 112 pmol/L in the corn oil group [$P > 0.3$]), second-phase insulin release (179 ± 66 pmol/L compared with 257 ± 122 pmol/L [$P > 0.3$]), and insulin sensitivity index (-0.03 ± 0.01 compared with -0.01 ± 0.01 [$\mu\text{mol/kg}\cdot\text{min}$ divided by pmol/L]; $P > 0.3$) were also similar in both groups after treatment. Fish oil lowered systolic blood pressure by 3.8 mm Hg more than control ($P = 0.04$) and lowered diastolic blood pressure by 2.0 mm Hg more than control ($P = 0.10$). After fish oil treatment, triglyceride levels decreased by 0.28 ± 0.08 mmol/L more than control ($P = 0.01$), and very-low-density lipoprotein cholesterol levels decreased by 0.13 ± 0.04 mmol/L more than control ($P = 0.01$). **CONCLUSION:** Fish oil, in doses that reduce blood pressure and lipid levels in hypertensive persons, does not adversely affect glucose metabolism.

Omega-6 fats-1.

Diabet Med. 1994 Mar;11(2):145-9.

[Related Articles, Links](#)

The use of gamma linolenic acid in the prevention and treatment of diabetic neuropathy.

Jamal GA.

Glasgow University Department of Neurology, Institute of Neurological Sciences, Scotland.

A substantial disturbance of the metabolism of the n-6 essential fatty acids (EFAs) exists in both human and experimental diabetes mellitus. The process of conversion of dietary linoleic acid to gammalinolenic, dihomogammalinolenic and arachidonic acids, and other polyunsaturates is inadequate in diabetic patients. Disturbances of these EFAs and the 1- and 2-series prostaglandins derived from them cause a variety of microvascular, haemorrhological, and other abnormalities leading to reduced blood flow and neural hypoxia. This will in turn produce an escalating cycle of further hypoxia through the generation of oxygen-free radicals and aggravation of neural capillary endothelial damage. Endoneurial hypoxia impairs axonal transport, produces demyelination, and reduces neural ATP-ase activity. Furthermore, depletion of polyunsaturated fatty acids derived from n-6 pathway may lead to abnormalities of myelin turnover, membrane-bound proteins (such as enzymes and receptors) and other axonal structural abnormalities. The disorders postulated here may synergistically interact with the metabolic changes described in both the glycosylation and the myoinositol hypotheses and may have important implications in the approach to treat diabetic neuropathy.

Omega-6 fats -2.

Diabetes Care. 1993 Jan;16(1):8-15.

[Related Articles, Links](#)

Treatment of diabetic neuropathy with gamma-linolenic acid. The gamma-Linolenic Acid Multicenter Trial Group.

Keen H, Payan J, Allawi J, Walker J, Jamal GA, Weir AI, Henderson LM, Bissessar EA, Watkins PJ, Sampson M, et al.

OBJECTIVE--To compare the effects of placebo and GLA on the course of mild diabetic neuropathy over 1 yr. **RESEARCH DESIGN AND METHODS--**We entered 111 patients with mild diabetic neuropathy from seven centers into a randomized, double-blind, placebo-controlled parallel study of GLA at a dose of 480 mg/day. MNCV, SNAP, CMAP, hot and cold thresholds, sensation, tendon reflexes, and muscle strength were assessed by standard tests in upper and lower limbs. **RESULTS--**For all 16 parameters, the change over 1 yr in response to GLA was more favorable than the change with placebo, and for 13 parameters, the difference was statistically significant. Sex, age, and type of diabetes did not influence the result, but treatment was more effective in relatively well-controlled than in poorly-controlled diabetic patients. **CONCLUSIONS--**GLA had a beneficial effect on the course of diabetic neuropathy.

Omega-6 fats -3

Prostaglandins Leukot Essent Fatty Acids. 1993 Jan;48(1):101-4.

[Related Articles, Links](#)

The effects of gamma-linolenic acid on breast pain and diabetic neuropathy: possible non-eicosanoid mechanisms.

Horrobin DF.

Gamma-linolenic acid (GLA) has recently been found to be beneficial in the management of breast pain and of diabetic neuropathy. GLA is a precursor of unsaturated fatty acids which are important in membrane structures, as second messengers in their own right and as precursors of eicosanoids. While the mechanisms of GLA action are likely to be complex, non-eicosanoid effects are probably of substantial importance. These effects include modification of membrane fluidity and of the functions of lipid-associated receptors and changes in the inositol cycle.

Omega-6 fats -4

Diabetologia. 2001 Nov;44(11):1973-88.

[Related Articles, Links](#)

Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy.

Cameron NE, Eaton SE, Cotter MA, Tesfaye S.

Diabetes mellitus is a major cause of peripheral neuropathy, commonly manifested as distal symmetrical polyneuropathy. This review examines evidence for the importance of vascular factors and their metabolic substrate from human and animal studies. Diabetic neuropathy is associated with risk factors for macrovascular disease and with other microvascular complications such as poor metabolic control, dyslipidaemia, body mass index, smoking, microalbuminuria and retinopathy. Studies in human and animal models have shown reduced nerve perfusion and endoneurial hypoxia. Investigations on biopsy material from patients with mild to severe neuropathy show graded structural changes in nerve microvasculature including basement membrane thickening, pericyte degeneration and endothelial cell hyperplasia. Arterio-venous shunting also contributes to reduced endoneurial perfusion. These vascular changes strongly correlate with clinical defects and nerve pathology. Vasodilator treatment in patients and animals improves nerve function. Early vasa nervorum functional changes are caused by the metabolic insults of diabetes, the balance between vasodilation and vasoconstriction is altered. Vascular endothelium is particularly vulnerable, with deficits in the major endothelial vasodilators, nitric oxide, endothelium-derived hyperpolarising factor and prostacyclin. Hyperglycaemia and dyslipidaemia driven oxidative stress is a major contributor, enhanced by advanced glycation end product formation and polyol pathway activation. These are coupled to protein kinase C activation and omega-6 essential fatty acid dysmetabolism. Together, this complex of interacting metabolic factors accounts for endothelial dysfunction, reduced nerve perfusion and function. Thus, the evidence emphasises the importance of vascular dysfunction, driven by metabolic change, as a cause of diabetic neuropathy, and highlights potential therapeutic approaches.

Omega-6 fats -5

Am J Clin Nutr. 2000 Jan;71(1 Suppl):386S-92S.

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Prevention of nerve conduction deficit in diabetic rats by polyunsaturated fatty acids.

Head RJ, McLennan PL, Raederstorff D, Muggli R, Burnard SL, McMurchie EJ.

CSIRO, Human Nutrition, Adelaide, Australia, and F Hoffmann-La Roche AG, Vitamin Research and Technology Department, Basel, Switzerland. richard.head@hsn.csiro.au

The influence of diets containing gamma-linolenic acid (GLA; 18:3n-6) on sciatic nerve conduction velocity (NCV) was determined in diabetic rats. NCV was lower in diabetic rats fed diets supplemented with olive oil or sunflower seed oil than in nondiabetic rats; rats supplemented with GLA during a 5-wk diabetic period, however, did not exhibit significantly lower NCV. The mean proportion of the phospholipid fatty acid linoleic acid (18:2n-6) was higher in the sciatic nerves of diabetic rats than in the nondiabetic groups irrespective of dietary lipid treatment. Additionally, the proportion of linoleic acid was higher in the diabetic rats fed sunflower oil than in all other groups. Dietary GLA supplementation did not significantly influence the fatty acid composition of nerve membrane phospholipids and there was no obvious correlation between the fatty acid composition of nerve membrane phospholipids and NCV. The content of fructose and glucose in sciatic nerves was higher, whereas that of myo-inositol was lower, in diabetic rats than in nondiabetic rats; however, this was not significantly influenced by dietary GLA. GLA administration did not significantly influence Na(+)-K(+)-exchanging ATPase or ouabain binding activity in sciatic nerve preparations, both of which remained nonsignificantly different in the diabetic and nondiabetic groups. The results suggest that dietary GLA can prevent the deficit in NCV induced by diabetes and that this effect is independent of the nerve phospholipid fatty acid profile, sugar and polyol content, Na(+)-K(+)-exchanging ATPase activity, and ouabain binding.

GLA may prevent the deficit in NCV indirectly, possibly by its role as a precursor of vasodilatory prostaglandins. These results confirm that GLA is the active component of evening primrose oil.

Pantethine-1

Clin Ter. 1989 Mar 31;128(6):411-22.

[Related Articles, Links](#)

**[Pantethine, diabetes mellitus and atherosclerosis. Clinical study of 1045 patients]
Donati C, Bertieri RS, Barbi G.**

After a review of the clinical studies on the treatment of diabetic patients with pantethine, the authors discuss the results obtained in a postmarketing surveillance (PMS) study on 1045 hyperlipidemic patients receiving pantethine (900 mg/day on average). Of these patients, 57 were insulin-dependent (Type I) and 241 were non insulin-dependent (Type II) diabetics. Beyond the epidemiological considerations made possible by a PMS study, the authors show that pantethine brought about a statistically significant and comparable improvement of lipid metabolism in the three groups of patients, with very good tolerability. Pantethine should therefore be considered for the treatment of lipid abnormalities also in patients at risk such as those with diabetes mellitus.

Pantethine-2

Clin Ter. 1989 Mar 31;128(6):411-22.

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**[Pantethine, diabetes mellitus and atherosclerosis. Clinical study of 1045 patients]
Donati C, Bertieri RS, Barbi G.**

After a review of the clinical studies on the treatment of diabetic patients with pantethine, the authors discuss the results obtained in a postmarketing surveillance (PMS) study on 1045 hyperlipidemic patients receiving pantethine (900 mg/day on average). Of these patients, 57 were insulin-dependent (Type I) and 241 were non insulin-dependent (Type II) diabetics. Beyond the epidemiological considerations made possible by a PMS study, the authors show that pantethine brought about a statistically significant and comparable improvement of lipid metabolism in the three groups of patients, with very good tolerability. Pantethine should therefore be considered for the treatment of lipid abnormalities also in patients at risk such as those with diabetes mellitus.

Pantothenic Acid (vitamin B5) -1

Diabetes. 1988 Oct;37(10):1335-9.

[Related Articles, Links](#)

Insulin effects on pantothenic acid uptake in isolated perfused working hearts from diabetic rats.

Lopaschuk GD.

Pantothenic acid uptake was studied in isolated working hearts from spontaneously diabetic BB Wistar and streptozocin-induced diabetic (STZ-D) rats. If insulin treatment was stopped for a 24-h period from spontaneously diabetic rats, a significant decrease in the rate of pantothenic uptake was noted (from 147.3 +/- 5.0 to 110.8 +/- 10.6 nmol.g-1 dry wt.30 min-1). Pantothenic acid uptake rates were also reduced in 48-h STZ-D rats (118.0 +/- 6.1 nmol.g-1 dry wt.30 min-1, compared to 158.2 +/- 5.3 in control rats). The decrease in pantothenic acid uptake in all diabetic animals occurred whether hearts were perfused with 1.2 mM palmitate or 1.2 mM palmitate and 11 mM glucose. If insulin (500 microU/ml) was added to the perfusion medium of hearts from spontaneously diabetic rats perfused with palmitate and glucose, a significant increase in pantothenic acid uptake was noted (from 110.8 +/- 10.6 to 167.0 +/- 9.4 nmol.g-1 dry wt.30 min-1). Insulin had no significant effect on pantothenic acid uptake in hearts from spontaneously diabetic rats perfused with palmitate alone. In STZ-D rats, insulin added to hearts perfused with palmitate and glucose resulted in a small but significant increase in pantothenic acid uptake (from 118.0 +/- 6.1 to 130.6 +/- 4.0 nmol.g-1 dry wt.30 min-1). Insulin had

no effect on pantothenic acid uptake in control hearts perfused either in the presence or absence of glucose. These data suggest that insulin, in the presence of glucose, can increase pantothenic acid uptake in diabetic rats.

P1. Norbiato G, Bevilacqua M . Effects of potassium supplementation on insulin binding and insulin action in human obesity: protein-modified fast and refeeding. Eur J Clin Invest. 1984 Dec;14(6):414-9.

To investigate the role of potassium deficiency in the development of glucose intolerance during caloric deprivation, potassium balance was maintained within normality with oral potassium supplementation in a group of obese subjects who underwent protein-modified fast and the results of the study of carbohydrate metabolism (oral glucose test, insulin receptors on monocytes and peripheral glucose utilization as assessed by euglycaemic clamp) were compared with those obtained in a group of obese subjects admitted to protein-modified fast without potassium supplementation. Caloric deprivation without oral potassium supplementation was followed by a negative potassium balance and a decrease of serum potassium levels; a decrease of the peripheral levels of insulin along with an increase in insulin receptors and a striking reduction of peripheral glucose utilization were also observed. The maintenance of normal potassium balance and normal serum potassium levels with oral potassium-chloride supplementation was associated with higher peripheral levels of insulin (P less than 0.01) and improvement of peripheral glucose utilization (P less than 0.01) whereas the binding of insulin to monocytes was unchanged. **The data suggest that potassium depletion during protein-modified fast causes a decrease of the peripheral levels of insulin and a resistance to insulin action at the postreceptors sites which is reversed by potassium supply.**

Selenium 1

J Trace Elem Med Biol. 1998 Jul;12(2):91-5.

[Related Articles, Links](#)

Selenium, zinc and copper in plasma of patients with type 1 diabetes mellitus in different metabolic control states.

Ruiz C, Alegria A, Barbera R, Farre R, Lagarda J.

Laboratory of Nutrition and Food Chemistry, Faculty of Pharmacy, University of Valencia, Spain.

The Studies of selenium (Se), zinc (Zn) and copper (Cu) levels in diabetic patients have led to contradictory findings as the possible relationship between the degree of diabetic control and the changes in mineral contents. In the present study the plasma Cu, Se, and Zn contents of diabetic patients and healthy people were measured and the relationship between these contents and diabetic metabolic control, as determined by glycosylated hemoglobin (HbA1c), was studied. **The mean plasma Se content in diabetic patients was significantly lower than in controls ($p < 0.01$) and a negative correlation between the plasma contents of Se and HbA1c was found.** No statistically significant differences in plasma Zn contents, either between patients with type 1 diabetes mellitus and control, were found. A statistically significant sex difference in plasma Cu contents was observed in the control population. In females, statistically significant differences were found in plasma Cu contents between the control subjects and the diabetic patients with medium or poor metabolic control, as well as between diabetic patients with good and poor metabolic control. In males, the only statistically significant differences were between the control subjects and diabetic patients with poor metabolic control. The correlation between plasma contents of Cu and HbA1c is not significant.

Taurine1

Neurochem Res. 2004 Jan;29(1):143-50.

[Links](#)

Is taurine beneficial in reducing risk factors for diabetes mellitus?

Franconi F, Di Leo MA, Bennardini F, Ghirlanda G.

Department of Pharmacology and Center for Biotechnology Development and Biodiversity Research, University of Sassari, Italy. franconi@uniss.it

Taurine is a semiessential amino acid, and its deficiency is involved in retinal and cardiac degenerations. In recent years, it was found that diabetes mellitus (DM) is associated with taurine, and many *in vivo* experimental studies showed that taurine administration is able to reduce the alterations induced by DM in the retina, lens, and peripheral nerve, although its effects on diabetic kidney are dubious. Interestingly, long-term taurine supplementation reduces the mortality rate in diabetic rats. The mechanisms by which taurine exerts beneficial effects in DM are discussed below. Recently, it has been suggested that taurine deficiency may alter the endocrine pancreas "fetal programming," increasing the risk of insulin resistance in adult life. The bulk of experimental data suggests that taurine administration could be useful in the treatment of type 1 DM and in the prevention of insulin resistance.

Taurine2

Clin Chim Acta. 2003 Oct;336(1-2):129-35.

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Inhibition of lipid peroxidation, protein glycation and elevation of membrane ion pump activity by taurine in RBC exposed to high glucose.

Nandhini TA, Anuradha CV.

Department of Biochemistry, Faculty of Science, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

BACKGROUND: Supplementation of taurine, a sulfur containing amino acid has been found to be beneficial in counteracting oxidative stress and in preventing experimental diabetic neuropathy, nephropathy and retinopathy. Taurine has its own capacity to prevent the suppression of membrane-bound Na(+)/K(+)ATPase activity and prevent Ca(2+) overload. This study was undertaken to test whether taurine can reduce lipid peroxidation and glycosylation and can increase the Na(+)/K(+)- and Ca(2+)-ATPase activities in high glucose-treated red blood cells (RBC). **METHODS:** Washed normal human RBC were incubated in phosphate-buffered saline with normal (6 mmol/l) or high glucose concentrations (45 mmol/l), with and without 50-150 micromol/l taurine in a shaking water bath at 37 degrees C for 24 h. Lipid peroxidation, glycated hemoglobin, glucose utilization and Na(+)/K(+)- and Ca(2+)-ATPase activities were determined in the glucose-treated human RBC. **RESULTS:** Taurine significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. Stimulation of glucose utilization by RBC was significant in the presence of taurine both in normal and high glucose-treated RBC. The activities of Na(+)/K(+)- and Ca(2+)-ATPases in RBC membranes were significantly lowered in high glucose-treated RBC. Taurine treatment significantly prevented the reduction in activities of Na(+)/K(+)- and Ca(2+)-ATPases activities in high glucose-treated RBC. **CONCLUSIONS:** The results show that taurine is important for the physiological functions of RBCs and the effects of taurine on glucose-treated RBC may have potential therapeutic relevance in diabetes.

Taurine3

Taurine prevents apoptosis induced by high ambient glucose in human tubule renal cells.

Verzola D, Bertolotto MB, Villaggio B, Ottonello L, Dallegri F, Frumento G, Berruti V, Gandolfo MT, Garibotto G, Deferran G.

Department of Internal Medicine, University of Genoa, Italy.

BACKGROUND: Hyperglycemia selectively triggers apoptosis in tubule and endothelial cells. Taurine, a conditionally essential amino acid, is abundant in several tubule segments, but its role has not been defined fully. It can serve as an osmolyte or as an endogenous antioxidant. Taurine metabolism is altered in diabetes mellitus, with extracellular and intracellular pools reduced. It is still unknown whether taurine can play a role as a protective agent in apoptosis induced by high glucose in tubular cells. **METHODS:** Apoptosis (by annexin V binding and the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling method), cellular reactive oxygen species (ROS) formation (by fluorescent probe 2'-7' dichlorofluorescein diacetate and FACScan flow cytometry), and Bcl-2 and Bax proteins (by immunostaining) were studied in a human proximal tubular cell line (HK-2) grown in a medium with physiologic (5.5 mM) or high (30 mM) glucose concentrations for 48 hours. In separate experiments, taurine (3-24 mM) was added to the media. **RESULTS:** The exposure of human tubule cells to 30 mM glucose for 48 hours resulted in a significant increase in apoptosis compared with 5.5 mM glucose (35 +/- 8% vs. 6 +/- 3%, $p < 0.001$). Thirty mM mannitol failed to induce the effects of high glucose. High glucose-mediated apoptosis was associated with a decrease in the expression of Bcl-2 (-87%) and a twofold increase in the expression of Bax protein. Taurine had a dose-dependent effect in preventing high-glucose-induced apoptosis (-78%, $p < 0.001$ at 24 mM). Moreover, with taurine, intracellular ROS decreased by 34% ($p < 0.05$), and changes in intracellular ROS formation induced by taurine at 24 hours predicted the variations in the apoptotic index at 48 hours ($r = 0.87$, $p < 0.02$). Other antioxidants, such as glutathione and N-acetylcysteine, also attenuated the high glucose-induced apoptosis. **CONCLUSION:** These results demonstrate that taurine attenuates hyperglycemia-induced apoptosis in human tubular cells via an inhibition of oxidative stress. Taurine might act as an endogenous antioxidant in tubule cells and could exert a beneficial effect in preventing tubulointerstitial injury in diabetic nephropathy.

Taurine4

Diabetes Metab Res Rev. 2001 Sep-Oct;17(5):330-46.

[Related Articles, Links](#)



The role of taurine in diabetes and the development of diabetic complications.

Hansen SH.

Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Denmark.
shhansen@rh.dk

The ubiquitously found beta-amino acid taurine has several physiological functions, e.g. in bile acid formation, as an osmolyte by cell volume regulation, in the heart, in the retina, in the formation of N-chlorotaurine by reaction with hypochlorous acid in leucocytes, and possibly for intracellular scavenging of carbonyl groups. Some animals, such as the cat and the C57BL/6 mouse, have disturbances in taurine homeostasis. The C57BL/6 mouse strain is widely used in diabetic and atherosclerotic animal models. In diabetes, the high extracellular levels of glucose disturb the cellular osmoregulation and sorbitol is formed intracellularly due to the intracellular polyol pathway, which is suspected to be one of the key processes in the development of diabetic late complications and associated cellular dysfunctions. Intracellular accumulation of sorbitol is most likely to

cause depletion of other intracellular compounds including osmolytes such as myo-inositol and taurine. When considering the clinical complications in diabetes, several links can be established between altered taurine metabolism and the development of cellular dysfunctions in diabetes which cause the clinical complications observed in diabetes, e.g. retinopathy, neuropathy, nephropathy, cardiomyopathy, platelet aggregation, endothelial dysfunction and atherosclerosis. Possible therapeutic perspectives could be a supplementation with taurine and other osmolytes and low-molecular compounds, perhaps in a combinational therapy with aldose reductase inhibitors. Copyright 2001 John Wiley & Sons, Ltd.

Taurine5

Am J Physiol Endocrinol Metab. 2003 Oct;285(4):E744-53. Epub 2003 Jun 10.

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N-acetylcysteine and taurine prevent hyperglycemia-induced insulin resistance in vivo: possible role of oxidative stress.

Haber CA, Lam TK, Yu Z, Gupta N, Goh T, Bogdanovic E, Giacca A, Fantus IG.

Department of Medicine, Mount Sinai Hospital, 60 Murray Street, Toronto, Ontario, Canada M5G 1X5.

Exposure to high concentrations of glucose and insulin results in insulin resistance of metabolic target tissues, a characteristic feature of type 2 diabetes. High glucose has also been associated with oxidative stress, and increased levels of reactive oxygen species have been proposed to cause insulin resistance. To determine whether oxidative stress contributes to insulin resistance induced by hyperglycemia in vivo, nondiabetic rats were infused with glucose for 6 h to maintain a circulating glucose concentration of 15 mM with and without coinfusion of the antioxidant N-acetylcysteine (NAC), followed by a 2-h hyperinsulinemic-euglycemic clamp. High glucose (HG) induced a significant decrease in insulin-stimulated glucose uptake [tracer-determined disappearance rate (Rd), control 41.2 +/- 1.7 vs. HG 32.4 +/- 1.9 mg. kg⁻¹. min⁻¹, P < 0.05], which was prevented by NAC (HG + NAC 45.9 +/- 3.5 mg. kg⁻¹. min⁻¹). Similar results were obtained with the antioxidant taurine. Neither NAC nor taurine alone altered Rd. HG caused a significant (5-fold) increase in soleus muscle protein carbonyl content, a marker of oxidative stress that was blocked by NAC, as well as elevated levels of malondialdehyde and 4-hydroxynonenal, markers of lipid peroxidation, which were reduced by taurine. In contrast to findings after long-term hyperglycemia, there was no membrane translocation of novel isoforms of protein kinase C in skeletal muscle after 6 h. These data support the concept that oxidative stress contributes to the pathogenesis of hyperglycemia-induced insulin resistance.

Taurine6

Can J Physiol Pharmacol. 1999 Oct;77(10):749-54.

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Taurine attenuates hypertension and improves insulin sensitivity in the fructose-fed rat, an animal model of insulin resistance.

Anuradha CV, Balakrishnan SD.

Department of Biochemistry, Annamalai University, Annamalai Nagar, Tamil Nadu, India.

Fructose feeding induces moderate increases in blood pressure levels in normal rats, which is associated with hyperinsulinemia, insulin resistance, and impaired glucose tolerance. Increased vascular resistance, sodium retention, and sympathetic overactivity have been proposed to contribute to the blood pressure elevation in this model. Taurine, a sulphur-containing amino acid, has been reported to have antihypertensive and sympatholytic

actions. In the present study, the effects of taurine on blood pressure, plasma levels of glucose and insulin, glucose tolerance, and renal function were studied in fructose-fed rats. Fructose-fed rats had higher blood pressure and elevated plasma levels of insulin and glucose. The plasma glucose levels were higher in fructose-fed rats than in controls at 15, 30, and 60 min after the oral glucose load. Treatment with 2% taurine in drinking water prevented the blood pressure elevation and attenuated the hyperinsulinemia in fructose-fed rats. The exaggerated glucose levels in response to the oral glucose load was also prevented by taurine administration. Thus, taurine supplementation could be beneficial in circumventing metabolic alterations in insulin resistance.

Vanadium-1

J Clin Endocrinol Metab. 2001 Mar;86(3):1410-7.

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Vanadyl sulfate improves hepatic and muscle insulin sensitivity in type 2 diabetes.

Cusi K, Cukier S, DeFronzo RA, Torres M, Puchulu FM, Redondo JC.

University of Texas Health Science Center, San Antonio, Texas 78284, USA. cusi@uthscsa.edu

Vanadyl sulfate (VOSO₄) is an oxidative form of vanadium that in vitro and in animal models of diabetes has been shown to reduce hyperglycemia and insulin resistance. Small clinical studies of 2- to 4-week duration in type 2 diabetes (T2DM) have led to inconsistent results. To define its efficacy and mechanism of action, 11 type 2 diabetic patients were treated with VOSO₄ at a higher dose (150 mg/day) and for a longer period of time (6 weeks) than in previous studies. Before and after treatment we measured insulin secretion during an oral glucose tolerance test, and endogenous glucose production (EGP) and whole body insulin-mediated glucose disposal using the euglycemic insulin clamp technique combined [3-(3)H]glucose infusion. Treatment significantly improved glycemic control: fasting plasma glucose (FPG) decreased from 194 +/- 16 to 155 +/- 15 mg/dL, hemoglobin A(1c) decreased from 8.1 +/- 0.4 to 7.6 +/- 0.4%, and fructosamine decreased from 348 +/- 26 to 293 +/- 12 micromol/L (all P < 0.01) without any change in body weight. Diabetics had an increased rate of EGP compared with nondiabetic controls (4.1 +/- 0.2 vs. 2.7 +/- 0.2 mg/kg lean body mass.min; P < 0.001), which was closely correlated with FPG (r = 0.56; P < 0.006). Vanadyl sulfate reduced EGP by about 20% (P < 0.01), and the decline in EGP was correlated with the reduction in FPG (r = 0.60; P < 0.05). Vanadyl sulfate also caused a modest increase in insulin-mediated glucose disposal (from 4.3 +/- 0.4 to 5.1 +/- 0.6 mg/kg lean body mass x min; P < 0.03), although the improvement in insulin sensitivity did not correlate with the decline in FPG after treatment (r = -0.16; P = NS). Vanadyl sulfate treatment lowered the plasma total cholesterol (223 +/- 14 vs. 202 +/- 16 mg/dL; P < 0.01) and low density lipoprotein cholesterol (141 +/- 14 vs. 129 +/- 14 mg/dL; P < 0.05), whereas 24-h ambulatory blood pressure was unaltered. We conclude that VOSO₄ at maximal tolerated doses for 6 weeks improves hepatic and muscle insulin sensitivity in T2DM. The glucose-lowering effect of VOSO₄ correlated well with the reduction in EGP, but not with insulin-mediated glucose disposal, suggesting that liver, rather than muscle, is the primary target of VOSO₄ action at therapeutic doses in T2DM.

Vanadium-2

J Clin Invest. 1995 Jun;95(6):2501-9.

[Related Articles, Links](#)

Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with non-insulin-dependent diabetes mellitus.

Cohen N, Halberstam M, Shlimovich P, Chang CJ, Shamoon H, Rossetti L.

Department of Medicine, Albert Einstein College of Medicine, New York 10461, USA.

We examined the in vivo metabolic effects of vanadyl sulfate (VS) in non-insulin-dependent diabetes mellitus (NIDDM). Six NIDDM subjects treated with diet and/or sulfonylureas were examined at the end of three consecutive periods: placebo for 2 wk, VS (100 mg/d) for 3 wk, and placebo for 2 wk. Euglycemic hyperinsulinemic (30 mU/m².min) clamps and oral glucose tolerance tests were performed at the end of each study period. Glycemic control at baseline was poor (fasting plasma glucose 210 +/- 19 mg/dl; HbA1c 9.6 +/- 0.6%) and improved after treatment (181 +/- 14 mg/dl [P < 0.05], 8.8 +/- 0.6%, [P < 0.002]); fasting and post-glucose tolerance test plasma insulin concentrations were unchanged. After VS, the glucose infusion rate during the clamp was increased (by approximately 88%, from 1.80 to 3.38 mg/kg.min, P < 0.0001). This improvement was due to both enhanced insulin-mediated stimulation of glucose uptake (rate of glucose disposal [Rd], +0.89 mg/kg.min) and increased inhibition of HGP (-0.74 mg/kg.min) (P < 0.0001 for both). Increased insulin-stimulated glycogen synthesis (+0.74 mg/kg.min, P < 0.0003) accounted for > 80% of the increased Rd after VS, and the improvement in insulin sensitivity was maintained after the second placebo period. The Km of skeletal muscle glycogen synthase was lowered by approximately 30% after VS treatment (P < 0.05). These results indicate that 3 wk of treatment with VS improves hepatic and peripheral insulin sensitivity in insulin-resistant NIDDM humans. These effects were sustained for up to 2 wk after discontinuation of VS.

Vanadium-3

Metabolism. 1996 Sep;45(9):1130-5.

[Related Articles, Links](#)

Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus.

Boden G, Chen X, Ruiz J, van Rossum GD, Turco S.

Division of Endocrinology/Diabetes/Metabolism and the General Clinical Research Center, Temple University Schools of Medicine and Pharmacy, Philadelphia, PA, USA.

The safety and efficacy of vanadyl sulfate (VS) was tested in a single-blind, placebo-controlled study. Eight patients (four men and four women) with non-insulin-dependent diabetes mellitus (NIDDM) received VS (50 mg twice daily orally) for 4 weeks. Six of these patients (four men and two women) continued in the study and were given a placebo for an additional 4 weeks. Euglycemic-hyperinsulinemic clamps were performed before and after the VS and placebo phases. VS was associated with gastrointestinal side effects in six of eight patients during the first week, but was well tolerated after that. VS administration was associated with a 20% decrease in fasting glucose concentration (from 9.3 +/- 1.8 to 7.4 +/- 1.4 mmol/L, P < .05) and a decrease in hepatic glucose output (HGO) during hyperinsulinemia (from 5.0 +/- 1.0 pre-VS to 3.1 +/- 0.9 micromol/kg x min post-VS, P < .02). The improvement in fasting plasma glucose and HGO that occurred during VS treatment was maintained during the placebo phase. VS had no significant effects on rates of total-body glucose uptake, glycogen synthesis, glycolysis, carbohydrate (CHO) oxidation, or lipolysis during euglycemic-hyperinsulinemic clamps. We conclude that VS at the dose used was well tolerated and resulted in modest reductions of fasting plasma glucose and hepatic insulin resistance. However, the safety of larger doses and use of vanadium salts for longer periods remains uncertain.

Vanadium-4

Diabetes. 1996 May;45(5):659-66.

[Related Articles, Links](#)

Oral vanadyl sulfate improves insulin sensitivity in NIDDM but not in obese nondiabetic subjects.

We compared the effects of oral vanadyl sulfate (100 mg/day) in moderately obese NIDDM and nondiabetic subjects. Three-hour euglycemic-hyperinsulinemic (insulin infusion 30 mU / m / min) clamps were performed after 2 weeks of placebo and 3 weeks of vanadyl sulfate treatment in six nondiabetic control subjects (age 37 +/-

3 years; BMI 29.5 +/- 2.4 kg/m²) and seven NIDDM subjects (age 53 +/- 2 years; BMI 28.7 +/-1.8 kg/m²). Glucose turnover ([3-3 H]glucose), glycolysis from plasma glucose, glycogen synthesis, and whole-body carbohydrate and lipid oxidation were evaluated. Decreases in fasting plasma glucose (by approximately 1.7 mmol/l) and HbA_{1c} (both P < 0.05) were observed in NIDDM subjects during treatment; plasma glucose was unchanged in control subjects. In the latter, the glucose infusion rate (GIR) required to maintain euglycemia (40.1 +/- 5.7 and 38.1 +/- 4.8 micromol / kg fat-free mass FFM / min) and glucose disposal (Rd) (41.7 +/- 5.7 and 38.9 +/-4.7 micromol / kg FFM / min) were similar during placebo and vanadyl sulfate administration, respectively. Hepatic glucose output (HGO) was completely suppressed in both studies. In contrast, in NIDDM subjects, vanadyl sulfate increased GIR approximately 82% (17.3 +/- 4.7 to 30.9 +/- 2.7 micromol / kg FFM / min, P < 0.05); this improvement in insulin sensitivity was due to both augmented stimulation of Rd (26.0 +/- 4.0 vs. 33.6 +/- 2.22 micromol / kg FFM / min, P < 0.05) and enhanced suppression of HGO (7.7 +/- 3.1 vs. 1.3 +/- 0.9 micromol / kg FFM / min, P < 0.05). Increased insulin-stimulated glycogen synthesis accounted for >80% of the increased Rd with vanadyl sulfate (P < 0.005), but plasma glucose flux via glycolysis was unchanged. In NIDDM subjects, vanadyl sulfate was also associated with greater suppression of plasma free fatty acids (FFAs) (P < 0.01) and lipid oxidation (P < 0.05) during clamps. The reduction in HGO and increase in Rd were both highly correlated with the decline in plasma FFA concentrations during the clamp period (P < 0.001). In conclusion, small oral doses of vanadyl sulfate do not alter insulin sensitivity in nondiabetic subjects, but it does improve both hepatic and skeletal muscle insulin sensitivity in NIDDM subjects in part by enhancing insulin's inhibitory effect on lipolysis. These data suggest that vanadyl sulfate may improve a defect in insulin signaling specific to NIDDM.

Vitamin B1-1

J Nutr Sci Vitaminol (Tokyo). 1987 Dec;33(6):421-30.

[Related Articles, Links](#)

Blood thiamine levels in outpatients with diabetes mellitus.

Saito N, Kimura M, Kuchiba A, Itokawa Y.

Department of Geriatrics, Kochi Medical University, Japan.

In 46 diabetic outpatients consisting of 20 males and 26 females not given thiamine treatment, the blood thiamine level was 46.9 +/- 28.5 ng/ml (mean +/- SD) and only 23.9% of all cases had a value of more than the normal lower limit (50 ng/ml). Erythrocyte transketolase activity was 443.8 +/- 107.7 micrograms/ml/h and only 20.9% had a value of ore than the normal lower limit (50 micrograms/ml/h), and the erythrocyte TPP effect was 16.6 +/- 13.2%. Moreover, there was a significant positive correlation (r = 0.97) between the blood thiamine level and erythrocyte transketolase activity, and a significant inverse correlation (r = -0.525, r = -0.576) between blood thiamine level and/or erythrocyte transketolase activity and the erythrocyte TPP effect. In 24 diabetic outpatients consisting of 14 males and 10 females given thiamine treatment, the blood thiamine level was 96.5 +/- 44.5 ng/ml/h excluding one case (621.7 ng/ml), and it was higher than the normal lower limit in 83% of all cases. Erythrocyte transketolase activity was 513.9 +/- 133.4 micrograms/ml/h and it was higher than the normal lower limit in 58.3%. Erythrocyte TPP effect was 5.84 +/- 8.39%. There was also a significant positive correlation (r = 0.663) between blood thiamine level and erythrocyte transketolase activity, and a significant inverse correlation (r = 0.0668, r = 0.834) between blood thiamine level and/or erythrocyte transketolase activity and erythrocyte TPP effect. Blood thiamine level and erythrocyte transketolase activity were significantly higher in diabetic outpatients given thiamine treatment than in diabetic outpatients not given thiamine treatment, while the erythrocyte TPP effect was significantly lower in diabetic outpatients given thiamine treatment than in diabetic outpatients not given thiamine treatment. There was no direct relationship between the lowered response of patellar tendon reflex and the biochemical status of thiamine. From the above findings it was concluded that diabetic outpatients tend to have a low blood thiamine level, with low erythrocyte transketolase activity and high erythrocyte TPP effect, and showed marginal thiamine deficiency.

Vitamin B1-2

Jpn J Pharmacol. 1983 Feb;33(1):27-31.

[Related Articles, Links](#)

Effect of thiamine and thiamine levels on experimental alloxan induced diabetes mellitus.

Hobara R, Kato H, Sakamoto K.

The effects of thiamine (T) on diabetes mellitus (DM) and the T levels in the brain, heart, liver, kidneys, pancreas, muscle, adipose tissue and blood were measured. For the experimental DM model, alloxan (170 mg/kg, i.v.) was injected into male ddY mice and insulin was also administered for 5 days to prevent death by hyperglycemia (DM group). After 14 days, blood glucose level increased to 455 mg/dl, compared to 166 mg/dl in the normal control group (NC group). In the DM mice, the T level in the liver decreased to 7.71 micrograms/g, compared to 16.29 micrograms/g in the NC group. The T levels in the heart, pancreas, muscle and adipose tissue increased to 18.63 micrograms/g, 3.99 micrograms/g, 2.53 micrograms/g and 5.07 micrograms/g in the DM group, compared to 14.99 micrograms/g, 3.27 micrograms/g, 1.98 micrograms/g and 4.04 micrograms/g in the NC group, respectively. The T levels in the brain and kidney were 2.38 micrograms/g and 14.00 micrograms/g in the DM group, compared to 2.34 micrograms/g and 13.72 micrograms/g in the NC group, respectively. But, in the heart, an active form of a T co-enzyme decreased to 27%, compared to 95% for the NC group. These results indicate a T deficiency or an endogenous T deficiency in the DM group. All DM mice without insulin treatment died within 7 days but about 40% of the mice survived up to 14 days with the administration of T.

Vitamin B6-1

Free Radic Biol Med. 2002 Dec 15;33(12):1615-21.

[Related Articles, Links](#)



Effect of high-glucose levels on protein oxidation in cultured lens cells, and in crystalline and albumin solution and its inhibition by vitamin B6 and N-acetylcysteine: its possible relevance to cataract formation in diabetes.

Jain AK, Lim G, Langford M, Jain SK.

Caddo Magnet High School, Shreveport, LA 71130, USA. sjain@lsuhsc.edu

Diabetic patients have elevated levels of glucose in their blood and other body fluids. This project studied the effect of high-glucose concentrations (HG) on the protein oxidation in cultured lens cells and in crystalline protein solution. In addition, we also examined the effect of HG on the oxidation and turbidity (aggregation) of albumin protein solution. This study also examined whether vitamin B6 [pyridoxine (P), pyridoxamine (PM)] or n-acetylcysteine (NAC) is capable of preventing protein oxidation similar to that seen in cataracts. For cell culture studies, rabbit lens cells were cultured in control or HG medium at 37 degrees C for 2 d. For studies with protein solution, a buffered solution of serum albumin or crystalline protein was incubated with normal glucose (5 mM) or HG (50-100 mM) in a water bath at 37 degrees C for 4 d. All treatments were carried out with and without the addition of P, PM, or NAC. We found significantly higher levels of carbonyl protein (an index of protein oxidation) in HG-treated compared with normal glucose-treated lens cells and in crystalline protein solution. P, PM, and NAC significantly decreased the protein oxidation in lens cells and crystalline protein solution. We also found significantly higher levels of protein oxidation and turbidity (an index of protein aggregation) and its inhibition by P, PM, and NAC in HG-treated compared with normal glucose-treated albumin solution. This suggests that HG can cause the oxidation and modification of proteins in the lens, and that vitamin B6 and NAC supplementation may be helpful in slowing the oxidation of lens proteins. This study

explains the cause of early cataract development and the potential benefit of supplementation with vitamin B6 and NAC in the prevention of the development of cataract among the diabetic population.

Vitamin B6-2

Diabetes Obes Metab. 1999 Jul;1(4):221-5.

[Related Articles, Links](#)



Effect of diabetes on vitamin B6 requirement in experimental animals.

Okada M, Shibuya M, Yamamoto E, Murakami Y.

Faculty of Health and Living Sciences, Naruto University of Education, Takashima 772-8502, Naruto, Japan.
mailto:okada@naruto-u.ac.jp

AIM: In the diabetic state, energy must be supplied mainly by amino acids and fat; therefore the metabolic processes are very similar to those of animals fed a high-protein diet. Vitamin B6-dependent enzymes, which are highly involved in amino acid metabolism, are important in diabetics. We investigated vitamin B6 content, and aspartate aminotransferase and glycogen phosphorylase activities, in several tissues of streptozotocin-induced diabetic and control rats. METHODS: The rats were fed a vitamin B6-free diet and administered an equivalent amount of pyridoxine based on body weight. RESULTS: Vitamin B6 content in all tissues examined, except for the liver, was lower in the diabetics than in controls. Aspartate aminotransferase activity was higher in the liver of diabetics than in the controls, but not in the other tissues. Glycogen phosphorylase activity in the gastrocnemius muscle of diabetics decreased to two-thirds of the control level. CONCLUSIONS: These data might indicate that diabetic animals should have a higher intake of vitamin B6 because a diabetic state can lead to a vitamin B6-deficiency.

Vitamin B6-3

Biochem Biophys Res Commun. 1991 Aug 30;179(1):615-9.

[Related Articles, Links](#)

A deficiency of vitamin B6 is a plausible molecular basis of the retinopathy of patients with diabetes mellitus.

Ellis JM, Folkers K, Minadeo M, VanBuskirk R, Xia LJ, Tamagawa H.

Department of Medicine, Titus County Hospital, Mt. Pleasant, Texas.

Eighteen patients with diabetes mellitus, some of whom had variously retinopathy, pregnancy, and the carpal tunnel syndrome, and were variously treated with steroids and vitamin B6, have been overviewed for periods of 8 months to 28 years. We have established an association of a deficiency of vitamin B6 with diabetes by monitoring the specific activity of the erythrocyte glutamic oxaloacetic transaminase and again by the association with the carpal tunnel syndrome (C.T.S.). It has been known for a decade that C.T.S. is caused by a B6 deficiency. The absence of retinopathy in vitamin B6-treated diabetic patients over periods of 8 months - 28 years appears monumental. These observations are like discovery and constitute a basis for a new protocol to establish the apparent relationship of a deficiency of vitamin B6 as a molecular cause of diabetic neuropathy. Blindness and vision are so important that the strength or weakness of the observations are not important; the conduct of a new protocol is important.

Vitamin B6-4

Am J Obstet Gynecol. 1977 Mar 15;127(6):599-602.

[Related Articles, Links](#)

Vitamin B6 treatment of gestational diabetes mellitus: studies of blood glucose and plasma insulin.

Spellacy WN, Buhi WC, Birk SA.

Thirteen women with late pregnancy gestational diabetes mellitus were tested with an intravenous glucose tolerance test and both blood glucose and plasma insulin levels were measured. Each woman was then treated with 100 mg. of vitamin B6 per day for 2 weeks and the intravenous glucose tolerance test was then repeated. There was a statistically significant improvement in the glucose tolerance curve after the vitamin B6 treatment, with a lowering of blood glucose levels at all points on the curve except for the 5 minute value. This glucose effect occurred despite an unchanged or lowered plasma insulin level. These results suggest that a relative deficiency in vitamin B6 is associated with some cases of gestational diabetes mellitus and that the replacement of this vitamin improves the metabolic state. The low vitamin B6 levels appear to alter metabolic pathways which result in a lowering of the biologic activity of endogenous insulin.

Vitamin B12-1

J Intern Med. 2003 Nov;254(5):455-63.

[Related Articles, Links](#)



Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial.

Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, Donker AJ, Stehouwer CD.

OBJECTIVE: Metformin is a key treatment option in type 2 diabetes. However, metformin may decrease vitamin B12 levels and increase levels of homocysteine, a cardiovascular risk factor. We investigated whether 16 weeks of treatment with metformin affects serum concentrations of homocysteine, folate and vitamin B12 in subjects with type 2 diabetes treated with insulin. **DESIGN:** Placebo-controlled, randomized trial. **Measurements:** at baseline and 16 weeks later. **SETTING:** This trial was conducted in the outpatient clinics of three general hospitals in The Netherlands. **SUBJECTS:** A total of 745 patients with type 2 diabetes, treated with insulin and not known with a contraindication for the use of metformin, were approached; 390 gave informed consent and entered the study. Thirty-seven subjects dropped out (12 placebo and 25 metformin users). **INTERVENTION:** Addition of metformin or placebo to insulin therapy. **PRIMARY OUTCOME PARAMETERS:** Serum homocysteine, folate, vitamin B12, indices of glycaemic control and body weight. **RESULTS:** Amongst those who completed 16 weeks of treatment, metformin use, as compared with placebo, was associated with an increase in homocysteine of 4% (0.2 to 8; P=0.039) and with decreases in folate [-7% (-1.4 to -13); P=0.024] and vitamin B12 [-14% (-4.2 to -24); P<0.0001]. In addition, the increase in homocysteine could be explained by the decreases in folate and vitamin B12. **CONCLUSION:** In patients with type 2 diabetes, 16 weeks of treatment with metformin reduces levels of folate and vitamin B12, which results in a modest increase in homocysteine. The clinical significance of these findings remains to be investigated.

Vitamin B12-2

Ann Clin Lab Sci. 2002 Summer;32(3):279-86.

[Related Articles, Links](#)

Association between homocysteinemia and renal function in patients with type 2 diabetes mellitus.

Ozmen B, Ozmen D, Turgan N, Habif S, Mutaf I, Bayindir O.

Homocysteinemia is an independent risk factor for cardiovascular disease, but information on its association

with type 2 diabetes and mild renal dysfunction is limited. Plasma total homocysteine (tHcy) concentration is partly determined by renal plasma clearance. Serum cystatin C (Cys C) concentration has been introduced as a marker of renal function, specifically as an indicator of glomerular filtration rate (GFR). The aim of this study was to explore the relationships among tHcy, creatinine clearance (Ccr), serum Cys C, and microalbuminuria in a population with type 2 diabetes. Fasting plasma tHcy, serum homocysteine-related vitamins (folate and vitamin B12), serum Cys C, serum creatinine, urine microalbumin, and creatinine clearance were determined in 75 type 2 diabetic patients and 40 healthy control subjects. The patients were assigned to two groups based on urinary albumin excretion (UAE): normoalbuminuric (NAU, UAE < 30 mg/24 hr, n = 35) and microalbuminuric (MAU, UAE 30-300 mg/24 hr, n = 40). Ccr was calculated using the Cockcroft-Gault formula. Plasma Hcy levels were determined by HPLC with fluorescence detection and serum Cys C by automated particle enhanced immunoturbidimetry. Plasma tHcy levels were significantly higher in normoalbuminuric and microalbuminuric patients than in controls (10.64 +/- 0.53, 13.29 +/- 0.78, 6.91 +/- 0.37 mmol/L, respectively). Serum Cys C levels in microalbuminuric diabetics were higher than in normoalbuminurics and controls (1.36 +/- 0.06, 1.12 +/- 0.04, 1.10 +/- 0.06 mg/L, respectively). Positive correlations were noted between tHcy and Cys C levels in normoalbuminuric and microalbuminuric diabetics ($r = 0.72$, $r = 0.64$, respectively). Homocysteine and creatinine concentrations were correlated in both diabetic groups ($r = 0.89$, $r = 0.93$, NAU and MAU, respectively). Elevated plasma total homocysteine concentrations in type 2 diabetics suggest an association between homocysteinemia and deterioration of renal function, evidenced by increased serum creatinine and Cys C, Ccr, and microalbuminuria. These findings implicate homocysteinemia in the relationship between diabetic nephropathy and cardiovascular complications of diabetes.

Vitamin B12-3

Diabet Med. 2001 Mar;18(3):185-92.

[Related Articles, Links](#)



Relation between homocysteinaemia and diabetic neuropathy in patients with Type 2 diabetes mellitus.

Ambrosch A, Dierkes J, Lobmann R, Kuhne W, Konig W, Luley C, Lehnert H.

Institute of Clinical Chemistry, University Hospital Magdeburg, Germany. aambrosch@hotmail.com

AIMS: Limited data are available on determinants of diabetic neuropathy as its pathogenesis is multifactorial. Since homocysteine exhibits toxic effects on vascular endothelial cells, the association between homocysteine and the prevalence of neuropathy in Type 2 diabetes mellitus was investigated. METHODS: A total of 65 Type 2 diabetic patients were consecutively enrolled into the study. Neuropathy was diagnosed according to clinical symptoms, clinical examination, electrophysiological sensory testing and autonomic function testing. With regard to homocysteine-related parameters, plasma homocysteine, folate, vitamin B12, vitamin B6 and renal function (creatinine, creatinine clearance, cystatin C) were measured, and the C677T polymorphism of the methylenetetrahydrofolate reductase gene was determined. RESULTS: Forty-three of the Type 2 diabetic patients were classified as suffering from neuropathy. Both patient groups were comparable with regard to demographic data, blood pressure, glucose metabolism, renal function and homocysteine-related vitamins. In contrast, homocysteine levels ($P = 0.04$) and the frequency of hyperhomocysteinemia (≥ 15 micromol/l) ($P = 0.01$) were significantly increased in neuropathic patients. In a logistic regression model with neuropathy as dependent variable, homocysteine (adjusted for creatinine, homocysteine-related vitamins, HbA1c and duration of diabetes) was the only significant variable associated with the prevalence of neuropathy (odds ratio for homocysteine per 5 micromol/l increase: 2.60 (95% confidence interval 1.07-6.33)). CONCLUSION: The data indicate that homocysteine is independently associated with the prevalence of diabetic neuropathy in a collective of Type 2 diabetic patients. A larger, prospective study would be desirable to clarify the role of homocysteine in the pathogenesis of diabetic neuropathy.

Vitamin C-1

Sinclair AJ, Taylor PB . Low plasma ascorbate levels in patients with type 2 diabetes mellitus consuming adequate dietary vitamin C. 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 $\mu\text{mol l}^{-1}$) and dehydroascorbate (27.6 +/- 6.4 $\mu\text{mol l}^{-1}$) levels were significantly lower in patients vs in controls (68.8 +/- 36.0 and 31.8 +/- 4.8 $\mu\text{mol l}^{-1}$, 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)

Vitamin C-2

Paolisso G, D'Amore A. Plasma vitamin C affects glucose homeostasis in healthy subjects and in non-insulin-dependent diabetics. Am J Physiol. 1994 Feb;266(2 Pt 1):E261-8.

In aged healthy ($n = 10$) and non-insulin-dependent (type II) diabetic ($n = 10$) subjects matched for age [67.3 +/- 0.5 vs. 68.0 +/- 0.4 yr, $P =$ not significant (NS)], body mass index (25.7 +/- 0.7 vs. 26.0 +/- 0.2 kg/m^2 , $P =$ NS), gender ratio [6 males (M)/4 females (F) vs. 5 M/5 F], and mean arterial blood pressure (104 +/- 6 vs. 105 +/- 9 mmHg, $P =$ NS), we determined the changes in insulin secretion and action after vitamin C infusion and the relative increase in plasma vitamin C levels. At the highest vitamin C infusion rate (0.9 mmol/min) the **increase in plasma vitamin C levels did not affect B cell response to glucose, but it improved Conard's K values and whole body glucose disposal in healthy subjects and in diabetic patients. In both groups of subjects vitamin C-mediated increase in insulin action was mainly due to an improvement in nonoxidative glucose metabolism.** After fasting, plasma vitamin C levels correlated with basal whole body glucose disposal ($r = -0.44$, $P < 0.05$; $n = 20$). After vitamin C infusion, percent change in plasma vitamin C level correlated with the percent decline in membrane microviscosity ($r = 0.53$, $P < 0.01$; $n = 20$) and increase in whole body glucose disposal ($r = 0.63$, $P < 0.003$; $n = 20$). In conclusion, **plasma vitamin C levels seem to play a role in the modulation of insulin action in aged healthy and diabetic subjects.**

Vitamin D-1

Br J Nutr. 1998 Apr;79(4):315-27.

[Related Articles, Links](#)

Inadequate vitamin D status: does it contribute to the disorders comprising syndrome 'X'?

Boucher BJ.

Environmental factors are important in the aetiology of glucose intolerance, type II diabetes and IHD. The lack of vitamin D, which is necessary for adequate insulin secretion, relates demographically to increased risk of myocardial infarction. These disorders are connected, degenerative vascular disease increasing with glucose intolerance and diabetes and, with its risk factors, comprising syndrome 'X'. Evidence is presented suggesting that vitamin D deficiency may be an avoidable risk factor for syndrome 'X', adding another preventative measure to current recommendations which are aimed at reducing the worldwide epidemic of these disorders. Experimentally, vitamin D deficiency progressively reduces insulin secretion; glucose intolerance follows and becomes irreversible. Relationships between vitamin D status, glucose tolerance and 30 min insulin secretion

during oral glucose tolerance tests are reported in British Asians; insulin secretion, but not glycaemia, improving with short-term supplementation. Studies showing reduction in blood pressure and in risk of heart attack and diabetes with exercise (usually outdoor), rarely consider the role of vitamin D status. Glycaemia and insulin secretion in elderly European men, however, relate to vitamin D status, independent of season or physical activity. Prolonged supplementation can improve glycaemia. Hypertension improves with vitamin D treatment with or without initial deficiency. Vitamin D status and climate are reviewed as risk factors for myocardial infarction; the risk reducing with altitude despite increasing cold. Glycaemia and fibrinogenaemia improve with insulin secretion increases in summer. Variation in vitamin D requirements could arise from genetic differences in vitamin D processing since bone density can vary with vitamin D-receptor genotype. Vitamin D receptors are present in islet beta cells and we report insulin secretion in healthy Asians differing profoundly with the Apa I genotype, being independent of vitamin D status. Those at risk of vitamin D deficiency include the elderly, those living indoors or having a covered-up style of dress, especially dark-skinned immigrants, and pregnant women, and these are groups recognized as being at increased risk of diabetes.

Vitamin E-1

Eur J Endocrinol. 1997 Sep;137(3):234-9.

[Related Articles, Links](#)

EJE Online

Vitamin E and nicotinamide have similar effects in maintaining residual beta cell function in recent onset insulin-dependent diabetes (the IMDIAB IV study)

Pozzilli P, Visalli N, Cavallo MG, Signore A, Baroni MG, Buzzetti R, Fioriti E, Mesturino C, Fiori R, Romiti A, Giovannini C, Lucentini L, Matteoli MC, Crino A, Teodonio C, Paci F, Amoretti R, Pisano L, Suraci C, Multari G, Suppa M, Sulli N, De Mattia G, Faldetta MR, Suraci MT.

Department of Diabetes and Metabolism, St Bartholomew's Hospital Medical College, London, UK.

OBJECTIVE: Protection of residual beta cell function at the time of diagnosis of insulin-dependent diabetes mellitus (IDDM) by intensive insulin therapy and the addition of nicotinamide (NA) has been established. The objective of this study was to evaluate the effect of a free oxygen radical scavenger such as vitamin E (Vit E) on residual beta cell function and parameters of metabolic control in patients with recent onset IDDM undergoing intensive insulin therapy. **DESIGN:** The effect of Vit E was compared with that of NA (control group) in a randomized multicentre trial. **METHODS:** Eighty-four IDDM patients between 5 and 35 years of age (mean age 15.8 +/- 8.4 (s.d.) years) entered a one year prospective study. One group of patients (n = 42) was treated with Vit E (15 mg/kg body weight/day) for one year; the other group (n = 42) received NA for one year (25 mg/kg body weight/day). All patients were under intensive insulin therapy with three to four injections a day. Basal and stimulated (1 mg i.v. glucagon) C-peptide secretion, glycosylated haemoglobin and insulin dose were evaluated at diagnosis and at three-monthly intervals up to one year. **RESULTS:** Preservation and slight increase of C-peptide levels at one year compared with diagnosis were obtained in the two treated patient groups. No statistically significant differences were observed in basal or stimulated C-peptide levels between the two groups of patients for up to one year after diagnosis. Glycosylated haemoglobin and insulin dose were also similar between the two groups; however patients receiving Vit E under the age of 15 years required significantly more insulin than NA-treated patients one year after diagnosis (P < 0.04). **CONCLUSIONS:** Our data indicate that Vit E and NA possess similar effects in protecting residual beta cell function in patients with recent onset IDDM. Since their putative mechanism of protection on beta cell cytotoxicity is different, combination of these two vitamins may be envisaged for future trials of intervention at IDDM onset.

Zinc1

Tang X, Shay NF. Zinc has an insulin-like effect on glucose transport mediated by

phosphoinositol-3-kinase and Akt in 3T3-L1 fibroblasts and adipocytes. J Nutr. 2001 May;131(5):1414-20.

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Zinc has insulin-like effects on cells, including promotion of both lipogenesis and glucose transport. The relationship between zinc and the stimulation of glucose transport is unclear. We hypothesize that zinc affects the insulin-signaling pathway. In this study, the effect of zinc on glucose transport and insulin signaling was examined in 3T3-L1-preadipocytes and -adipocytes. Treatment of cells with up to 200 micromol/L zinc significantly increased glucose transport ($P < 0.05$). The effect of zinc on adipocytes was greater than on preadipocytes, and the effect of zinc plus insulin was greater than that of either insulin or zinc alone. Cytochalasin D, which disrupts actin filaments, attenuated the increase of glucose transport induced by zinc or insulin ($P < 0.05$). At 100 nmol/L, wortmannin, the phosphoinositide (PI) 3-kinase inhibitor, decreased basal glucose transport and blocked zinc-stimulated glucose transport in both cell types ($P < 0.05$). H7, an inhibitor of protein kinase C, did not reduce basal glucose transport but decreased zinc-induced glucose transport ($P < 0.05$). Zinc increased tyrosine phosphorylation of the insulin receptor beta subunit of both preadipocytes and adipocytes after 5-10 min of treatment ($P < 0.05$). Zinc at 200 micromol/L did not affect tyrosine phosphorylation of insulin receptor substrate (IRS)-1 or -2; further, there was no effect of zinc on the association of the p85 subunit of PI 3-kinase and IRS-1. Zinc significantly increased serine-473 phosphorylation of Akt in both preadipocytes and adipocytes ($P < 0.05$). The PI 3-kinase inhibitor, wortmannin, totally blocked the effect of zinc on Akt activation. Hence, it appears that **zinc can induce an increase in glucose transport into cells and potentiate insulin-induced glucose transport, likely acting through the insulin-signaling pathway.**

Zinc2

Pol Arch Med Wewn. 1995 Sep;94(3):228-34.

[Related Articles, Links](#)

Activity of superoxide dismutase in erythrocytes and leukocytes and levels of zinc and copper in blood of patients with diabetes. Effect of diabetic treatment on examined parameters **Zbronska H, Grzeszczak W, Jendryczko A, Zbronski R, Kuzniewicz R.**

The purpose of the present work was to assess the relationship of leukocyte and erythrocyte superoxide dismutase activity to its cofactors concentrations i.e. zinc and copper in plasma and erythrocyte in diabetic patients and treatment variability. 104 patients were included in the study. 23 persons were in the control group. All patients were divided into 2 groups (NIDDM and IDDM). Patients with NIDDM were divided into 3 subgroups depending on treatment (insulin, gliclazide, dietary treated). In all groups, there were assessed following parameters: the leucocyte and erythrocyte SOD activity according to the method of Misra and Fridovich, and zinc and copper concentrations in plasma and erythrocyte, which were measured by flame absorption spectrophotometry. Statistical analysis was performed using the CRISP program. CONCLUSION: 1. **The leukocyte and erythrocyte superoxide dismutase activity is significantly lowered in diabetes mellitus.** 2. **In diabetic patients both in type I and type II as in the healthy people, there is a close correlation between SOD activity and its cofactors i.e. zinc and copper erythrocyte concentrations.** 3. **Insulin and gliclazide treatment increases SOD activity and delays late diabetic complications.**

J Periodontol. 1997 Aug;68(8):713-9.

[Related Articles, Links](#)

Treatment of periodontal disease in diabetics reduces glycosylated hemoglobin.

Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, Genco RJ.

Periodontal disease is a common infection-induced inflammatory disease among individuals suffering from diabetes mellitus. The purpose of this study was to assess the effects of treatment of periodontal disease on the level of metabolic control of diabetes. A total of 113 Native Americans (81 females and 32 males) suffering

from periodontal disease and non-insulin dependent diabetes mellitus (NIDDM) were randomized into 5 treatment groups. Periodontal treatment included ultrasonic scaling and curettage combined with one of the following antimicrobial regimens: 1) topical water and systemic doxycycline, 100 mg for 2 weeks; 2) topical 0.12% chlorhexidine (CHX) and systemic doxycycline, 100 mg for 2 weeks; 3) topical povidone-iodine and systemic doxycycline, 100 mg for 2 weeks; 4) topical 0.12% CHX and placebo; and 5) topical water and placebo (control group). Assessments were performed prior to and at 3 and 6 months after treatment and included probing depth (PD), clinical attachment level (CAL), detection of *Porphyromonas gingivalis* in subgingival plaque and determination of serum glucose and glycated hemoglobin (HbA1c). After treatment all study groups showed clinical and microbial improvement. The doxycycline-treated groups showed the greatest reduction in probing depth and subgingival *Porphyromonas gingivalis* compared to the control group. In addition, all 3 groups receiving systemic doxycycline showed, at 3 months, significant reductions ($P < \text{or} = 0.04$) in mean HbA1c reaching nearly 10% from the pretreatment value. Effective treatment of periodontal infection and reduction of periodontal inflammation is associated with a reduction in level of glycated hemoglobin. Control of periodontal infections should thus be an important part of the overall management of diabetes mellitus patients.