

Abstracts-Diaxinol

1. Free Radic Biol Med. 1999 Aug;27(3-4):309-14.

Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial.

Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ, Dietze GJ, Rett K.

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.

2. Exp Clin Endocrinol Diabetes. 1996;104(3):284-8.

Improvement of insulin-stimulated glucose-disposal in type 2 diabetes after repeated parenteral administration of thioctic acid.

Jacob S, Henriksen EJ, Tritschler HJ, Augustin HJ, Dietze GJ.

Insulin resistance of skeletal muscle glucose uptake is a prominent feature of Type II diabetes (NIDDM); therefore, pharmacological intervention should aim to improve insulin sensitivity. Thioctic acid (TA), a naturally occurring compound, was shown to enhance glucose utilization in various experimental models after acute and chronic

administration. It also increased insulin-stimulated glucose disposal in patients with NIDDM after acute administration. This pilot study was initiated to see whether this compound also augments glucose disposal in humans after repeated treatment. Twenty patients with NIDDM received TA (500 mg/ 500 ml NaCl, 0.9%) as daily infusions over a period of ten days. A hyperinsulinaemic, isoglycaemic glucose-clamp was done on day 0 and day 11. Parenteral administration of TA resulted in a significant increase of insulin-stimulated glucose-disposal by about 30% (metabolic clearance rate for glucose, 2.5 +/- 0.3 vs. 3.2 +/- 0.4 ml/kg/min and insulin-sensitivity-index: 3.5 +/- 0.5 vs. 4.7 +/- 0.4 mg/kg/microU/ml; $p < 0.05$, Wilcoxon-Rank-Sum-Test). There were no changes in fasting plasma levels for glucose or insulin; this can be explained, however, by the short period of treatment and observation. This is the first clinical study to show that a ten day administration of TA is able to improve resistance of insulin-stimulated glucose disposal in NIDDM. Experimental data suggest several mechanisms in the mode of action. As the present investigation was an uncontrolled pilot trial, the encouraging results call for controlled studies to further elucidate the clinical relevance of the findings and the mode of action of this compound.

3. Free Radic Biol Med. 1999 Jun;26(11-12):1495-500.

alpha-Lipoic acid decreases oxidative stress even in diabetic patients with poor glycemic control and albuminuria.

Borcea V, Nourooz-Zadeh J, Wolff SP, Klevesath M, Hofmann M, Urich H, Wahl P, Ziegler R, Tritschler H, Halliwell B, Nawroth PP.

In the present cross-sectional study, the influence of alpha-lipoic acid on markers of oxidative stress, assessed by measurement of plasma lipid hydroperoxides (ROOHs), and on the balance between oxidative stress and antioxidant defence, determined by the ratio ROOH/(alpha-tocopherol/cholesterol), was examined in 107 patients with diabetes mellitus. Patients receiving alpha-lipoic acid (600 mg/day for > 3 months) had significant lower ROOHs and a lower ROOH/(alpha-tocopherol/cholesterol) ratio than those without alpha-lipoic acid treatment [ROOH: 4.76 +/- 2.49 vs. 7.16 +/- 3.22 $\mu\text{mol/l}$; $p < .0001$] and [ROOH/(alpha-tocopherol/cholesterol): 1.37 +/- 0.72 vs. 2.16 +/- 1.17; $p < 0.0001$]. In addition, the influence of glycemic control and albuminuria on ROOHs and on the ratio of ROOH/(alpha-tocopherol/cholesterol) was examined in the presence and absence of alpha-lipoic acid treatment. Patients were subdivided into three groups based on (1) their HbA1 levels (< 7.5, 7.5-9.5, and > 9.5%) and (2) their urinary albumin concentrations (< 20, 20-200, and > 200 mg/l). Neither poor glycemic control, nor the presence of micro- or macroalbuminuria prevented the antioxidant effect of alpha-lipoic acid. Using stepwise multiple regression analysis, alpha-lipoic acid was found to be the only factor significantly predicting low ROOHs and a low ratio of ROOH/(alpha-tocopherol/cholesterol). These data provide evidence that treatment with alpha-lipoic acid improves significantly the imbalance between increased oxidative stress and depleted antioxidant defence even in patients with poor glycemic control and albuminuria.

4. Exp Clin Endocrinol Diabetes. 1999;107(7):421-30.

Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials.

Ziegler D, Reljanovic M, Mehnert H, Gries FA.

Diabetic neuropathy represents a major health problem, as it is responsible for substantial morbidity, increased mortality, and impaired quality of life. Near-normoglycaemia is now generally accepted as the primary approach to prevention of diabetic neuropathy, but is not achievable in a considerable number of patients. In the past two decades several medical treatments that exert their effects despite hyperglycaemia have been derived from the experimental pathogenetic concepts of diabetic neuropathy. Such compounds have been designed to improve or slow the progression of the neuropathic process and are being evaluated in clinical trials, but with the exception of alpha-lipoic acid (thioctic acid) which is available in Germany, none of these drugs is currently available in clinical practice. Here we review the current evidence from the clinical trials that assessed the therapeutic efficacy and safety of thioctic acid in diabetic polyneuropathy. Thus far, 15 clinical trials have been completed using different study designs, durations of treatment, doses, sample sizes, and patient populations. Within this variety of clinical trials, those with beneficial effects of thioctic acid on either neuropathic symptoms and deficits due to polyneuropathy or reduced heart rate variability resulting from cardiac autonomic neuropathy used doses of at least 600 mg per day. The following conclusions can be drawn from the recent controlled clinical trials. 1.) Short-term treatment for 3 weeks using 600 mg of thioctic acid i.v. per day appears to reduce the chief symptoms of diabetic polyneuropathy. A 3-week pilot study of 1800 mg per day given orally indicates that the therapeutic effect may be independent of the route of administration, but this needs to be confirmed in a larger sample size. 2.) The effect on symptoms is accompanied by an improvement of neuropathic deficits. 3.) Oral treatment for 4-7 months tends to reduce neuropathic deficits and improves cardiac autonomic neuropathy. 4.) Preliminary data over 2 years indicate possible long-term improvement in motor and sensory nerve conduction in the lower limbs. 5.) Clinical and postmarketing surveillance studies have revealed a highly favourable safety profile of the drug. Based on these findings, a pivotal long-term multicenter trial of oral treatment with thioctic acid (NATHAN I Study) is being conducted in North America and Europe aimed at slowing the progression of diabetic polyneuropathy using a clinically meaningful and reliable primary outcome measure that combines clinical and neurophysiological assessment.

5. Diabet Med. 1999 Dec;16(12):1040-3.

Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy.

Ruhnau KJ, Meissner HP, Finn JR, Reljanovic M, Lobisch M, Schutte K, Nehrdich D, Tritschler HJ, Mehnert H, Ziegler D.

AIMS: To evaluate the efficacy and safety of short-term oral treatment with the antioxidant thioctic acid (TA) on neuropathic symptoms and deficits in patients with

Type 2 diabetes mellitus with symptomatic polyneuropathy. **METHODS:** Patients were randomly assigned to oral treatment with 600 mg of TA t.i.d. (n = 12) or placebo (n = 12) for 3 weeks. Neuropathic symptoms (pain, burning, paraesthesiae, and numbness) in the feet were scored at weekly intervals and summarized as a Total Symptom Score (TSS). The Hamburg Pain Adjective List (HPAL) and the Neuropathy Disability Score (NDS) were assessed at baseline and day 19. **RESULTS:** At baseline the TSS, HPAL, and NDS were not significantly different between the groups. The TSS in the foot decreased from baseline to day 19 by -3.75 +/- 1.88 points (-47%) in the TA group and by -1.94 +/- 1.50 points (-24%) in the placebo group (P= 0.021 for TA vs. placebo). The total HPAL score decreased from baseline to day 19 by -2.20 +/- 1.65 points (-60%) in the TA group and by -0.96 +/- 1.32 points (-29%) in the placebo group (P = 0.072 for TA vs. placebo). The NDS decreased by -0.27 +/- 0.47 points in the TA group, whereas it slightly increased by +0.18 +/- 0.4 points in the placebo group (P = 0.025 for TA vs. placebo). No differences between the groups were noted regarding the rates of adverse events. **CONCLUSIONS:** These preliminary findings indicate that oral treatment with 600 mg of TA t.i.d. for 3 weeks may improve symptoms and deficits resulting from polyneuropathy in Type 2 diabetic patients, without causing significant adverse reactions.

6. Diabetes Care. 1999 Aug;22(8):1296-301.

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.

Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K, Kerum G, Malessa R.

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 \pm 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, had no effect on neuropathic symptoms distinguishable from placebo to a clinically meaningful degree, possibly due to increasing intercenter variability in symptom scoring during the study. However, this 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.

7. Am J Hypertens. 2003 Mar;16(3):173-9.

Lipoic acid prevents hypertension, hyperglycemia, and the increase in heart mitochondrial superoxide production.

Midaoui AE, Elimadi A, Wu L, Haddad PS, de Champlain J.

BACKGROUND: The present study was designed to investigate whether the effects of dietary supplementation with alpha-lipoic acid could prevent the increase in mitochondrial superoxide production in the heart as well as the enhanced formation of advanced glycation end-products (AGE) that are associated with the development of hypertension and insulin resistance in chronically glucose-fed rats. **METHODS:** Sprague Dawley rats were either given or not given a 10% D-glucose solution to drink during 4 weeks, combined either with a normal chow diet or with alpha-lipoic acid supplemented diet. The oxidative stress was evaluated by measuring the heart mitochondrial superoxide production using the lucigenin chemiluminescence method. The formation of AGE was also assessed in plasma and aorta. **RESULTS:** Chronic administration of glucose resulted in a 29% increase in blood pressure, 30% increase in glycemia, 286% increase in insulinemia, and 408% increase in insulin resistance index. Chronic glucose feeding also resulted in a 22% greater mitochondrial superoxide anion production in heart and in an increase of 63% in AGE content in aorta. Increases in blood pressure, aorta AGE content and heart mitochondrial superoxide production were prevented in the rats fed glucose supplemented with lipoic acid. The simultaneous treatment with lipoic acid also attenuated the rise in insulin levels as well as in insulin resistance in the glucose fed rats. **CONCLUSIONS:** These findings demonstrate that alpha-lipoic acid supplementation prevents development of hypertension and hyperglycemia, presumably through its antioxidative properties, as reflected by prevention of an increase in heart mitochondrial superoxide anion production and in AGE formation in the aorta of chronically glucose treated rats.

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

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

Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J.

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

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

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

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

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.

10. J Nutr Biochem. 2002 Nov;13(11):690-697.

Role of chromium supplementation in Indians with type 2 diabetes mellitus.

Ghosh D, Bhattacharya B, Mukherjee B, Manna B, Sinha M, Chowdhury J, Chowdhury S.

Type 2 diabetes mellitus is a complex metabolic disorder with adverse cardiovascular risk. The role of micronutrients has not yet been well clarified in this condition, especially in India. THE OBJECTIVES OF THIS STUDY WERE TO: (1) evaluate chromium status in Indian subjects with type 2 diabetes mellitus, (2) assess the effect of chromium picolinate (200 &mgr;g trivalent chromium twice daily) administration on glycaemic control and lipid profile in these subjects and (3) comment on the possible mechanism of any beneficial effect noted above. Fifty subjects were studied in a double blind, placebo-controlled, crossover fashion, with each treatment arm (chromium/placebo) lasting 12 weeks and 4 weeks' wash-off period in between. 50 healthy age- and sex-matched volunteers served as controls. Serum chromium level appeared to be higher in the general population in our country compared to western countries (36.5-59.5 nmol/L as compared to 2.3-40.3 nmol/L) However, the local diabetics were found to have a lower serum chromium level than the healthy controls (32.3 nmol/L against 44.7 nmol/L; $p < 0.0001$) and a mean increase of 3.5 nmol/L was noted after 12 weeks of chromium supplementation that was, expectedly, not seen in the placebo phase ($p < 0.0001$). Significant improvement in glycaemic control was noted in the chromium-treated group (DeltaFasting serum glucose = 0.44 mmol/L, $p < 0.001$; DeltaPost-prandial serum glucose = 1.97 mmol/L, $p < 0.001$; Deltaglycated hemoglobin = 0.01; $p = 0.04$, in comparison to placebo) This was accompanied by a significant greater fall in fasting serum insulin in the chromium-treated group, $p < 0.05$. The change in lipid parameters (total serum cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides) did not show significant difference between the chromium and placebo groups. Clinically significant hematological, renal or hepatic toxicity were excluded by routine hemogram, serum urea, creatinine, alanine amino transferase (ALT) and alkaline phosphatase estimations. In conclusion, chromium supplementation seems to improve glycaemic control in type 2 diabetic patients, which appears to be due to an increase in insulin action rather than stimulation of insulin secretion.

11. J Nutr Sci Vitaminol (Tokyo). 1996 Dec;42(6):517-26.

A high biotin diet improves the impaired glucose tolerance of long-term spontaneously hyperglycemic rats with non-insulin-dependent diabetes

mellitus.

Zhang H, Osada K, Maebashi M, Ito M, Komai M, Furukawa Y.

The Otsuka Long-Evans Tokushima Fatty (OLETF) rat, serving as a spontaneously diabetic model with non-insulin-dependent diabetes mellitus (NIDDM), exhibits impaired glucose tolerance (IGT) at about 16 weeks of age. In this study, we investigated whether or not biotin, a water-soluble vitamin, improved the IGT of OLETF rats. To this end, we administered diets containing one of three levels of biotin, a high-biotin diet (BH), a normal-biotin diet (BN) and a basal-biotin diet (BB), to OLETF rats up to 24 weeks of age. An oral glucose tolerance test (OGTT) was performed four times between 13 and 22 weeks of age. The administration of a BH corrected the IGT of OLETF rats. Upon further investigation, we found that insulin secretion in the OLETF-BH rats was decreased to a significant extent, signaling that the hyperinsulinemia typical to the OLETF-BH rats had clearly improved. Body weights were significantly lower in the OLETF-BH group than in the other OLETF groups, even though the OLETF-BH rats showed a significantly higher average daily food intake. The body weight gain of the OLETF-BH rats followed the same tendency as the control-LETO (Long Evans Tokushima Otsuka) rats (LETO-BB and LETO-BN). These results demonstrate that a high-level biotin diet can improve the glucose handicap in NIDDM rats.

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

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.

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.

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

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

Halberstam M, Cohen N, Shlimovich P, Rossetti L, Shamon H.

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 HbA1c (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.

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

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

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

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.

15. J Ethnopharmacol. 1990 Oct;30(3):295-300.

Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin-dependent diabetes mellitus patients.

Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K, Shanmugasundaram ER.

The effectiveness of GS4, an extract from the leaves of *Gymnema sylvestre*, in controlling hyperglycaemia was investigated in 22 Type 2 diabetic patients on conventional oral anti-hyperglycaemic agents. GS4 (400 mg/day) was administered for 18-20 months as a supplement to the conventional oral drugs. During GS4 supplementation, the patients showed a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins, and conventional drug dosage could be decreased. Five of the 22 diabetic patients were able to discontinue their conventional drug and maintain their blood glucose homeostasis with GS4 alone. These data suggest that the beta cells may be regenerated/repared in Type 2 diabetic patients on

GS4 supplementation. This is supported by the appearance of raised insulin levels in the serum of patients after GS4 supplementation.

16. J Ethnopharmacol. 1990 Oct;30(3):281-94.

Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus.

Shanmugasundaram ER, Rajeswari G, Baskaran K, Rajesh Kumar BR, Radha Shanmugasundaram K, Kizar Ahmath B.

GS4, a water-soluble extract of the leaves of *Gymnema sylvestre*, was administered (400 mg/day) to 27 patients with insulin-dependent diabetes mellitus (IDDM) on insulin therapy. Insulin requirements came down together with fasting blood glucose and glycosylated haemoglobin (HbA1c) and glycosylated plasma protein levels. While serum lipids returned to near normal levels with GS4 therapy, glycosylated haemoglobin and glycosylated plasma protein levels remained higher than controls. IDDM patients on insulin therapy only showed no significant reduction in serum lipids, HbA1c or glycosylated plasma proteins when followed up after 10-12 months. GS4 therapy appears to enhance endogenous insulin, possibly by regeneration/revitalisation of the residual beta cells in insulin-dependent diabetes mellitus.