

## ABSTRACTS

## Testosterone

**Are major risk factors for myocardial infarction the major predictors of degree of coronary artery disease in men?**

Although numerous cross-sectional studies have reported associations of hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity with the presence of coronary artery disease (CAD), correlations of these risk factors for myocardial infarction (MI) with the degree or progression of CAD have been less consistent. Nevertheless, these risk factors are generally assumed to be major determinants not only of MI, but of the degree of CAD as well. The present study is an attempt to evaluate the relationship of major risk factors for MI to degree of CAD. From 182 men who underwent diagnostic coronary arteriography, the 154 with CAD were selected for study. These 154 patients were divided into 2 groups, those with hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity (n = 121) and those with none of these risk factors (n = 33). The mean degree of CAD in the group with risk factors for MI (44.4%) and in the group without (50.6%) was not significantly different (P = .15); nor was the increase in CAD with age augmented by the presence of these risk factors. On multiple regression analysis, none of these risk factors was associated with degree of CAD. Three other variables that were considered in this study, age, high-density lipoprotein-cholesterol (HDL-C), and free testosterone (FT), did show an independent association with degree of CAD. These findings, together with the findings of previous studies from other laboratories, raise the possibility that in men selected for coronary arteriography, age, HDL-C, and FT may be stronger predictors of degree of CAD than are blood pressure, cholesterol, diabetes, smoking, and body mass index (BMI).

*Metabolism. 2004 Mar;53(3):324-9*

**Endogenous sex hormones and progression of carotid atherosclerosis in elderly men.**

**BACKGROUND:** The burden of atherosclerosis especially afflicts the increasing older segment of the population. Recent evidence has emphasized a protective role of endogenous sex hormones in the development of atherosclerosis in aging men. **METHODS AND RESULTS:** We studied the association between endogenous sex hormones and progression of atherosclerosis in 195 independently living elderly men. Participants underwent measurements of carotid intima-media thickness (IMT) at baseline in 1996 and again in 2000. At baseline, serum concentrations of testosterone (total and free) and estradiol (total and free E2) were measured. Serum free testosterone concentrations were inversely related to the mean progression of IMT of the common carotid artery after adjustment for age (beta=-3.57; 95% CI, -6.34 to -0.80). Higher serum total and free E2 levels were related to progression of IMT of the common carotid artery after adjustment for age (beta=0.38; 95% CI, -0.11 to 0.86; and beta=0.018; 95% CI, -0.002 to 0.038, respectively). These associations were independent of body mass index, waist-to-hip ratio, presence of hypertension and diabetes, smoking, and serum cholesterol levels **CONCLUSIONS:** Low free testosterone levels were related to IMT of the common carotid artery in elderly men independently of cardiovascular risk factors.

*Circulation. 2004 May 4;109(17):2074-9. Epub 2004 Apr 19*

**The associations of endogenous testosterone and sex hormone-binding globulin with glycosylated hemoglobin levels, in community dwelling men. The Tromso Study.**

**OBJECTIVES:** Low levels of endogenous testosterone have been associated with increased risk of cardiovascular disease and atherosclerosis in men. Long-term hyperglycemia, as measured by glycosylated hemoglobin (HbA1c), is related to cardiovascular mortality, and HbA1c across its normal range is also positively related to coronary heart and cardiovascular disease mortality in men. We therefore undertook an analysis of the cross-sectional associations of total testosterone and SHBG levels with HbA1c levels, in a general population of 1419 men aged 25-84. **METHODS:** Total testosterone, sex hormone-binding globulin (SHBG) and HbA1c were measured by immuno-assay. Partial correlation and multiple regression analyses were used to estimate the associations between total testosterone and SHBG with HbA1c. Analyses of variance and covariance were used to compare men with or without diabetes. **RESULTS:** In age-adjusted partial correlation HbA1c was inversely associated with total testosterone (p<0.01) and SHBG (p<0.001). HbA1c was positively associated with body mass index (BMI) and waist circumference (WC) (p<0.001). In multiple regression analyses total testosterone, SHBG, age, number of cigarettes smoked, BMI and WC were independently associated with HbA1c levels. Men with a history of diabetes had lower levels of total testosterone in age-adjusted analyses (p<0.05) and lower levels of SHBG in both age- and WC-adjusted analyses (p<0.001 and p<0.01, respectively). **CONCLUSION:** Lower levels of total testosterone and SHBG were associated with increased HbA1c levels and diabetes independent of concomitant variations in obesity and body fat distribution.

*Diabetes Metab. 2004 Feb;30(1):29-34*

### **An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males.**

This clinical study investigated the possible associations of male sex hormone with the extensiveness of coronary artery lesions, coronary heart disease risk factors and ejection fraction of the heart. Ninety six Caucasian male subjects were recruited, 76 with positive and 20 with negative coronary angiograms. Early morning, prior to haemodynamic examination all of them had determined levels of total testosterone, free testosterone, free androgen index (FAI), sex hormone-binding globulin (SHBG), oestradiol, luteinizing hormone, follicle-stimulating hormone, plasma lipids, fibrinogen and glucose. The ejection fraction and the extensiveness of coronary lesions of each subject was assessed on the basis of x-ray examination results using Quantitative Coronary Angiography (QCA) and Left Ventricular Analysis (LVA) packages on the TCS Acquisition workstation, Medcon. Men with proven coronary heart disease had significantly lower levels of total testosterone (11.9 vs 21.2 nmol/l), free testosterone (45.53 vs 86.10 pmol/l), free androgen index (36.7 vs 47.3 IU) and oestradiol (109.4 vs 146.4 pmol/l). The level of testosterone was negatively associated with the DUKE Index. The most essential negative correlation was observed between SHBG and atherogenic lipid profile (low high-density lipoprotein, high triglycerides). Ejection fraction was substantially lower in patients (51.85 vs 61.30) (without prior myocardial infarction) with low levels of free-testosterone (23.85 vs. 86.10 pmol/l) and FAI (28.4 vs 47.3 IU). A negative correlation was observed between total testosterone, free testosterone, FAI and blood pressure, especially with diastolic pressure. Men with proven coronary atherosclerosis had lower levels of endogenous androgens than the healthy controls. For the first time in clinical settings it has been demonstrated that low levels of free-testosterone was characteristic for patients with low ejection fraction. Numerous hypotheses for this action can be proposed but all require a proper evaluation process. The main determinant of atherogenic plasma lipid was low levels of SHBG suggesting its main role in developing atherosclerotic lesions.

*J Med Invest. 2003 Aug;50(3-4):162-9*

### **Acute haemodynamic effects of testosterone in men with chronic heart failure.**

AIMS: Anabolic therapy with testosterone may be useful in the treatment of wasting associated with chronic heart failure but little is known about its cardiovascular actions. The aim of this study was to determine the acute haemodynamic effects of testosterone administration in men with heart failure. METHODS AND RESULTS: Twelve men with stable chronic heart failure were enrolled in a double-blind, randomised, placebo-controlled, cross-over trial. Subjects were given testosterone 60 mg or placebo via the buccal route and central haemodynamics were monitored over 6h, using a pulmonary flotation catheter. Subjects received the second treatment on day 2 and haemodynamic monitoring was repeated. Treatment was well tolerated. Compared with placebo, testosterone treatment resulted in a relative increase in cardiac output ( $p < 0.0001$ , ANCOVA), with maximum treatment effect after 180 min (10.3+/-4.6% increase from baseline,  $p = 0.035$ ; 95% CI 0.8-19.8). This was accompanied by reduction in systemic vascular resistance compared with baseline ( $p < 0.0001$ , ANCOVA), with maximum treatment effect also at 180 min (-17.4+/-9.6% from baseline,  $p = 0.085$ ; 95% CI -37.3 to +2.6). These maximal changes coincided with the peak elevation in serum bio-available testosterone. There was no significant change in any other haemodynamic parameter measured. CONCLUSIONS: Administration of testosterone increases cardiac output acutely, apparently via reduction of left ventricular afterload.

*Eur Heart J. 2003 May;24(10):909-15*

### **Administration of testosterone is associated with a reduced susceptibility to myocardial ischemia.**

This study investigated the impact of testosterone on myocardial ischemia-reperfusion injury and corresponding intracellular calcium ( $[Ca^{2+}]_i$ ) metabolism. Nonorchietomized mature male Wistar rats were randomly assigned to placebo, a single dose of testosterone undecanoate, or 5 $\alpha$ -dihydrotestosterone. In a further series, orchietomized rats were treated with placebo. After 2 wk of treatment, the hearts were removed and placed in a Langendorff setup. The isolated, buffer-perfused hearts were subjected to 30 min of no-flow ischemia and 30 min of reperfusion. Recovery of myocardial function was measured by analyzing pre- and postischemic left ventricular (LV) systolic/diastolic pressure and coronary perfusion pressure simultaneously, together with  $[Ca^{2+}]_i$  handling (aequorin luminescence). Calcium regulatory proteins were analyzed by Western blotting. LV weight/body weight ratio was increased after administration of testosterone vs. orchietomized rats. The recovery of contractile function was improved in testosterone-treated rats: at the end of the reperfusion, LV systolic pressure was higher and end-diastolic pressure was lower in testosterone-treated rats. End-ischemic  $[Ca^{2+}]_i$  and  $[Ca^{2+}]_i$  overload upon reperfusion was significantly lower in testosterone vs. orchietomized rats, too. However, levels of calcium regulatory proteins remained unaffected. In conclusion, administration of testosterone significantly improves recovery from global ischemia. These beneficial effects are associated with an attenuation of reperfusion induced  $[Ca^{2+}]_i$  overload.

*Endocrinology. 2003 Oct;144(10):4478-83. Epub 2003 Jul 10*

### **High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study.**

Androgens stimulate prostate cancer in vitro and in vivo. However, evidence from epidemiologic studies of an association between circulating levels of androgens and prostate cancer risk has been inconsistent. We investigated the association of serum levels of testosterone, the principal androgen in circulation, and sex hormone-binding globulin (SHBG) with risk in a case-control study

nested in cohorts in Finland, Norway and Sweden of 708 men who were diagnosed with prostate cancer after blood collection and among 2,242 men who were not. In conditional logistic regression analyses, modest but significant decreases in risk were seen for increasing levels of total testosterone down to odds ratio for top vs. bottom quintile of 0.80 (95% CI = 0.59-1.06; p(trend) = 0.05); for SHBG, the corresponding odds ratio was 0.76 (95% CI = 0.57-1.01; p(trend) = 0.07). For free testosterone, calculated from total testosterone and SHBG, a bell-shaped risk pattern was seen with a decrease in odds ratio for top vs. bottom quintile of 0.82 (95% CI = 0.60-1.14; p(trend) = 0.44). No support was found for the hypothesis that high levels of circulating androgens within a physiologic range stimulate development and growth of prostate cancer.

*Int J Cancer. 2004 Jan 20;108(3):418-24*

### **Reduced circulating androgen bioactivity in patients with prostate cancer.**

**BACKGROUND:** Previous studies on immunoreactive androgen levels in serum have revealed equivocal associations with the risk of prostate cancer (CaP). The aim of this study was to compare serum biological androgen activity between men with newly diagnosed CaP and age-matched men with benign prostatic hyperplasia (BPH). **METHODS:** Caucasian men with newly diagnosed, untreated CaP (n = 101) and age-matched patients with BPH (n = 103) were investigated. Serum androgen bioactivity (ABA) levels were measured using a recently developed recombinant cell bioassay. **RESULTS:** In comparison to men with BPH, CaP patients with Gleason score  $\geq 8$  (n = 16) had lower serum ABA (P < 0.05), and patients with Gleason score  $\leq 5$  (P < 0.05) or  $\geq 8$  (P = 0.07) displayed suppressed ABA levels in relation to serum testosterone. As the entire group, men with CaP (n = 101) had significantly lower serum ABA than age-matched men with BPH (n = 103): median 3.0 nM (range, 0.8-6.4 nM) versus 3.2 nM (range, 0.8-7.9 nM) testosterone equivalents, respectively (P < 0.005). By contrast, serum immunoreactive testosterone and SHBG concentrations and free androgen indices did not differ significantly between the two groups. **CONCLUSIONS:** Patients with CaP have lower serum ABA than controls with BPH, and men with low or high Gleason score display suppressed circulating ABA-to-testosterone ratio. These features may reflect interaction between variables such as the degree of tumor differentiation and tumor volume with androgen metabolism.

*Prostate. 2003 May 15;55(3):194-8*

## ABSTRACTS

### CoQ10

#### **Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction.**

In a randomized, double-blind, controlled trial, the effects of oral treatment with coenzyme Q10 (CoQ10, 120 mg/day), a bioenergetic and antioxidant cytoprotective agent, were compared for 1 year, on the risk factors of atherosclerosis, in 73 (CoQ, group A) and 71 (B vitamin group B) patients after acute myocardial infarction (AMI). After 1 year, total cardiac events (24.6 vs. 45.0%,  $p < 0.02$ ) including non-fatal infarction (13.7 vs. 25.3%,  $p < 0.05$ ) and cardiac deaths were significantly lower in the intervention group compared to control group. The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement, previous coronary artery disease and elapsed time from symptom onset to infarction at entry to study showed no significant differences between the two groups. Plasma level of vitamin E (32.4 +/- 4.3 vs. 22.1 +/- 3.6 umol/L) and high density lipoprotein cholesterol (1.26 +/- 0.43 vs. 1.12 +/- 0.32 mmol/L) showed significant ( $p < 0.05$ ) increase whereas thiobarbituric acid reactive substances, malondialdehyde (1.9 + 0.31 vs. 3.1 + 0.32 pmol/L) and diene conjugates showed significant reduction respectively in the CoQ group compared to control group. Approximately half of the patients in each group ( $n = 36$  vs. 31) were receiving lovastatin (10 mg/day) and both groups had a significant reduction in total and low density lipoprotein cholesterol compared to baseline levels. It is possible that treatment with CoQ10 in patients with recent MI may be beneficial in patients with high risk of atherothrombosis, despite optimal lipid lowering therapy during a follow-up of 1 year. Adverse effect of treatments showed that fatigue (40.8 vs. 6.8%,  $p < 0.01$ ) was more common in the control group than CoQ group.

*Mol Cell Biochem. 2003 Apr;246(1-2):75-82*

#### **Overview on coenzyme Q10 as adjunctive therapy in chronic heart failure. Rationale, design and end-points of "Q-symbio"--a multinational trial.**

Energy starvation of the myocardium is probably a dominant feature of heart failure and attention has been directed towards agents which may stabilize myocardial metabolism and maintain adequate energy stores. A reduced myocardial tissue content of the essential redox-component and natural antioxidant Coenzyme Q10 (CoQ10) has been detected in patients with heart failure and the observed level of CoQ10 deficiency was correlated to the severity of heart failure. CoQ10 fulfills various criteria of an obvious adjunct in patients with symptomatic heart failure: it is devoid of significant side effects and it improves symptoms and quality of life. Till this date, several double-blind placebo-controlled trials with CoQ10 supplementation in more than 1000 patients have been positive and statistically significant with respect to various clinical parameters, e.g. improvement in NYHA Class, exercise capacity and reduced hospitalisation frequency. Also treatment with CoQ10 led to a significant improvement of relevant hemodynamic parameters. In only 3 out of 13 double-blind studies comprising 10% of the total number of patients treated the results were neutral. Thus, based on the available controlled data CoQ10 is a promising, effective and safe approach in chronic heart failure. This is why a double-blind multicenter trial with focus on morbidity and mortality has been planned to start in 2003: Q-SYMBIO. Patients in NYHA classes III to IV ( $N=550$ ) receiving standard therapy are being randomized to treatment with CoQ10 100 mg t.i.d. or placebo in parallel groups. End-points in a short-term evaluation phase of 3 months include symptoms, functional capacity and biomarker status (BNP). The aim of a subsequent 2-year follow-up study is to test the hypothesis that CoQ10 may reduce cardiovascular morbidity (unplanned cardiovascular hospitalisation due to worsening heart failure) and mortality as a composite endpoint. This trial should help to establish the future role of CoQ10 as part of a maintenance therapy in patients with chronic heart failure.

*Biofactors. 2003;18(1-4):79-89*

#### **Anti-oxidant effects of coenzyme Q10 on experimental viral myocarditis in mice.**

We studied the effects of coenzyme Q10 (CoQ10) on mice with acute myocarditis inoculated with the encephalomyocarditis (EMC) virus with the analysis of indices of effects of oxidative injury and DNA damage in the myocardium. The mice were treated as follows: CoQ10 group ( $n = 118$ ); CoQ10 1.0 mg (0.1 mL) x 2/d (0.1 mg/g/d), control group ( $n = 128$ ); sham-liquid 0.1 mL x 2/d. The mice were injected intraperitoneally 1 day before and daily for 12 days after EMC virus inoculation. The expression of thioredoxin, a marker of oxidative stress overload, as well as 8-hydroxy-2'-deoxyguanosine, an established marker of DNA damage, in the myocardium was investigated. The survival rate was significantly higher ( $P < 0.01$ ) in the CoQ10 group (46.8%, 29/62) than in the control group (14.3%, 10/70). There were significant increases of CoQ9 and CoQ10 in the heart, which are the biologically active forms of CoQ in mice, and significant decrease of serum creatine kinase (CK)-MB in the CoQ10 group as compared with the control group. Histologic examination showed that the severity of myocarditis was less severe ( $P < 0.01$ ) in the CoQ10 group than in the control group. In addition, the up-regulation of myocardial thioredoxin with DNA damage, which was induced by the inflammatory stimuli by the virus, was suppressed by the CoQ10 treatment, which may reflect the anti-oxidant effects of CoQ10 treatment. Thus, pretreatment with CoQ10 may reduce the severity of viral myocarditis in mice associated with decreasing oxidative stress in the condition.

*J Cardiovasc Pharmacol. 2003 Nov;42(5):588-92*

### **Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure.**

**COENZYME Q10 IN PHYSICAL EXERCISE.** We identified eleven studies in which CoQ10 was tested for an effect on exercise capacity, six showed a modest improvement in exercise capacity with CoQ10 supplementation but five showed no effect. **COENZYME Q10 IN HYPERTENSION.** We identified eight published trials of CoQ10 in hypertension. Altogether in the eight studies the mean decrease in systolic blood pressure was 16 mm Hg and in diastolic blood pressure, 10 mm Hg. Being devoid of significant side effects CoQ10 may have a role as an adjunct or alternative to conventional agents in the treatment of hypertension. **COENZYME Q10 IN HEART FAILURE.** We performed a randomised double blind placebo-controlled pilot trial of CoQ10 therapy in 35 patients with heart failure. Over 3 months, in the CoQ10 patients but not in the placebo patients there were significant improvements in symptom class and a trend towards improvements in exercise time. **META-ANALYSIS OF RANDOMIZED TRIALS OF COENZYME Q10 IN HEART FAILURE.** In nine randomised trials of CoQ10 in heart failure published up to 2003 there were non-significant trends towards increased ejection fraction and reduced mortality. There were insufficient numbers of patients for meaningful results. To make more definitive conclusions regarding the effect of CoQ10 in cardiac failure we recommend a prospective, randomised trial with 200-300 patients per study group. Further trials of CoQ10 in physical exercise and in hypertension are recommended.

*Biofactors. 2003;18(1-4):91-100*

### **Statins lower plasma and lymphocyte ubiquinol/ubiquinone without affecting other antioxidants and PUFA.**

It has been shown that treating hypercholesterolemic patients (HPC) with statins leads to a decrease, at least in plasma, not only in cholesterol, but also in important non-sterol compounds such as ubiquinone (CoQ10), and possibly dolichols, that derive from the same biosynthetic pathway. Plasma CoQ10 decrease might result in impaired antioxidant protection, therefore leading to oxidative stress. In the present paper we investigated the levels in plasma, lymphocytes and erythrocytes, of ubiquinol and ubiquinone, other enzymatic and non-enzymatic lipophilic and hydrophilic antioxidants, polyunsaturated fatty acids of phospholipids and cholesterol ester fractions, as well as unsaturated lipid and protein oxidation in 42 hypercholesterolemic patients treated for 3 months. The patients were treated with different doses of 3 different statins, i.e. atorvastatin 10 mg (n = 10) and 20 mg (n = 7), simvastatin, 10 mg (n = 5) and 20 mg (n = 10), and pravastatin, 20 mg (n = 5) and 40 mg (n = 5). Simvastatin, atorvastatin and pravastatin produced a dose dependent plasma depletion of total cholesterol (t-CH), LDL-C, CoQ10H2, and CoQ10, without affecting the CoQ10H2/CoQ10 ratio. The other lipophilic antioxidants (d-RRR-alpha-tocopherol-vit E-, gamma-tocopherol, vit A, lycopene, and beta-carotene), hydrophilic antioxidants (vit C and uric acid), as well as, TBA-RS and protein carbonyls were also unaffected. Similarly the erythrocyte concentrations of GSH and PUFA, and the activities of enzymatic antioxidants (Cu,Zn-SOD, GPx, and CAT) were not significantly different from those of the patients before therapy. In lymphocytes the reduction concerned CoQ10H2, CoQ10, and vit E; other parameters were not investigated. The observed decline of the levels of CoQ10H2 and CoQ10 in plasma and of CoQ10H2, CoQ10 and vit E in lymphocytes following a 3 month statin therapy might lead to a reduced antioxidant capacity of LDL and lymphocytes, and probably of tissues such as liver, that have an elevated HMG-CoA reductase enzymatic activity. However, this reduction did not appear to induce a significant oxidative stress in blood, since the levels of the other antioxidants, the pattern of PUFA as well as the oxidative damage to PUFA and proteins resulted unchanged. The concomitant administration of ubiquinone with statins, leading to its increase in plasma, lymphocytes and liver may cooperate in counteracting the adverse effects of statins, as already pointed out by various authors on the basis of human and animal studies.

*Biofactors. 2003;18(1-4):113-24*

## ABSTRACTS

### Chromium

#### **Chromium and parenteral nutrition.**

Studies involving patients on total parenteral nutrition (TPN) led to conclusive documentation of the essential role of Cr in human nutrition. These patients developed severe diabetic symptoms including glucose intolerance, weight loss, impaired energy utilization, and nerve and brain disorders that were refractory to insulin. After addition of Cr to TPN fluids, diabetic symptoms were alleviated, and exogenous insulin was no longer required. Cr intake by healthy subjects consuming average Westernized diets is suboptimal; if these subjects experience severe physical trauma or other forms of stress, Cr status may be overtly compromised. Recommendations for daily Cr supplementation of 10-20 micrograms for patients on short-term TPN (< or = 1-3 mos) appear to be adequate. Stable patients on long-term TPN may receive ample Cr from that present in TPN fluids. Because of the variable nature of contaminating Cr, Cr intake and losses of TPN patients should be monitored.

*Nutrition. 1995 Jan-Feb;11(1 Suppl):83-6*

#### **Effect of chromium supplementation on glucose tolerance and lipid profile.**

**OBJECTIVES:** To investigate chromium status of the adult population in the western region of Saudi Arabia and the possibility of using serum chromium status measurement as indicator of this status. **METHODS:** The effect of chromium supplement on glucose tolerance and lipid profile was studied in 44 normal, free living adults. 200mg chromium/day as CrCl<sub>3</sub> or a placebo was given in a double blind cross-over study, with 8 weeks experimental periods. Fasting, 1 hour and 2 hour post glucose challenge (75 g of glucose) glucose, serum fructosamine, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, chromium and dietary intakes were estimated at the beginning and the end of each stage. **RESULTS:** Mean serum chromium increased significantly after supplement ( $P<.001$ ) indicating proper absorption of the element. Supplement did not effect the total cholesterol, however, the mean high-density lipoprotein-cholesterol level was significantly increased ( $P<.001$ ), the mean triglycerides levels significantly decreased ( $P<.001$ ), and the mean fructosamine level significantly decreased ( $P<.05$ ). In addition, chromium supplement effected 1 hour and 2 hour post glucose challenge glucose levels in subgroups of subjects with 2 hour glucose level > 10% above or below fasting level and significantly differing to it ( $P<.05$  in both cases), by decreasing or increasing them significantly ( $P<.05$  in all cases) so that the 2 hour mean became not significantly different to the fasting mean. Since no significant changes in weight, dietary intake or habits were found, and placebo had no effect, all noted biochemical changes were attributed to chromium. **CONCLUSION:** Improved glucose control, and lipid profile following chromium supplement suggests the presence of low chromium status in the studied population. However, serum chromium could not be recommended for use as an indicator of chromium status as subjects with widely varying levels responded favorably to the chromium supplement.

*Saudi Med J. 2000 Jan;21(1):45-50*

#### **Beneficial effects of chromium in people with type 2 diabetes, and urinary chromium response to glucose load as a possible indicator of status.**

No reliable method for the estimation of chromium (Cr) status is available yet. The aim of this study is to investigate the possibility of using urinary Cr response to glucose load as an indicator of Cr status. Seventy-eight non-insulin-dependent diabetes mellitus patients, were divided randomly into two groups and given Cr supplements as brewer's yeast and CrCl<sub>3</sub> sequentially with placebo in between, in a double-blind, crossover design of four stages, each lasting 8 wk. At the beginning and end of each stage, subjects were weighed, their dietary data and drug dosage recorded, and blood and urine samples collected for analysis of glucose and urinary chromium (fasting and 2 h post-75-g glucose load) and fructosamine. The mean urinary Cr after the glucose load was significantly higher than the fasting mean at zero time ( $p<0.01$ ). However, only 52 of the patients showed an obvious increase; the others showed a slight decrease or no change. Both supplements caused a significant increase in the means of urinary Cr and a significant decrease in the means of glucose and fructosamine. Only those subjects responding to Cr supplement by improved glucose control showed an increase in post-glucose-load urinary Cr over fasting level, after the supplement but not at zero time. Therefore, it was concluded that urinary Cr response to glucose load could be used as an indicator of Cr status.

*Biol Trace Elem Res. 2002 Feb;85(2):97-109*

#### **Antioxidant effects of chromium supplementation with type 2 diabetes mellitus and euglycemic subjects.**

To determine the effects of chromium (Cr) supplementations on oxidative stress of type 2 diabetes and euglycemic (EU) subjects, adult having HbA(1C) values of <6.0% (EU), 6.8-8.5% (mildly hyperglycemic, MH), and >8.5% (severely hyperglycemic, SH) were supplemented for 6 months with 1000 microg/day of Cr (as Cr yeast) or with a placebo. In the beginning, the levels of the plasma Cr in the MH and SH groups were 25-30% lower than those of the EU subjects. The values of thiobarbituric acid reactive substances (TBARS) and total antioxidative status (TAS) of the MH and SH groups were significantly higher than those of the EU ones. Following supplementations, the levels of plasma TBARS in the Cr groups of MH and SH groups were

significantly decreased (the inverse was found in the EU) and showed no significant changes in the placebo group. The levels of plasma TAS in the Cr groups of EU and MH were significantly decreased (the inverse was found in the SH) and showed no significant changes in the placebo group. No significant difference was found in the antioxidant enzyme (superoxide dismutase, glutathione peroxidase, catalase) activities during supplementations. These data suggest that Cr supplementation was an effective treatment strategy to minimize increased oxidative stress in type 2 diabetes mellitus patients whose HbA(1C) level was >8.5%, and the Cr in EU groups might act as a prooxidant.

*J Agric Food Chem. 2004 Mar 10;52(5):1385-9*

### **Concentrations of seven trace elements in different hematological matrices in patients with type 2 diabetes as compared to healthy controls.**

This study aimed to compare the trace element status of patients with type 2 diabetes (n = 53) with those of nondiabetic healthy controls (n = 50). The concentrations of seven trace elements were determined in the whole blood, blood plasma, erythrocytes, and lymphocytes of the study subjects. Vanadium and iron levels in lymphocytes were significantly higher in diabetic patients as compared to controls (p < 0.05 for iron and p < 0.01 for vanadium). In contrast, lower manganese (p < 0.01) and selenium (p < 0.01) concentrations were detected in lymphocytes derived from patients with type 2 diabetes versus healthy subjects. Furthermore, significantly lower chromium levels (p < 0.05) were found in the plasma of diabetic individuals as compared to controls. Trace element concentrations were not dependent on the degree of glucose control as determined by correlation analysis between HbA1c versus metal levels in the four blood fractions. In summary, this study primarily demonstrated that trace element levels in lymphocytes of patients with type 2 diabetes could deviate significantly from controls, whereas, in general, no considerable differences could be found when comparing the other fractions between both patient groups. Therefore, it seems reasonable to analyze metal levels in leukocytes to determine trace element status in patients with type 2 diabetes and perhaps in other diseases.

*Biol Trace Elem Res. 2001 Mar;79(3):205-19*

### **Chromium and insulin resistance.**

Since as early as the 50s of the last century, it has been known that chromium is essential for normal glucose metabolism. Too little chromium in the diet may lead to insulin resistance. However, there is still no standard against which chromium deficiency can be established. Nevertheless, chromium supplements are becoming increasingly popular. Various systematic reviews have been unable to demonstrate any effects of chromium on glycaemic regulation (possibly due partly to the low dosages used), but there is a slight reduction in body weight averaging 1 kg. In a double-blind randomised placebo-controlled trial in a Chinese population with type-2 diabetes mellitus, supplementation with 1000 micrograms of chromium led to a fall in the glycosylated haemoglobin level (HbA1c) by 2%. Toxic effects of chromium are seldom seen; recently, however, the safety of one of the dosage forms of chromium, chromium picolinate, has been questioned. One should be aware that individual patients with type-2 diabetes mellitus may have an increased risk of hypoglycaemic episodes when taking chromium supplements as self-medication.

*Ned Tijdschr Geneesk. 2004 Jan 31;148(5):217-20*

### **The effects of LDL reduction and HDL augmentation on physiologic and inflammatory markers.**

Cholesterol plays an important role in atherogenesis. Oxidized low-density lipoprotein cholesterol is harmful to arteries whereas high-density lipoprotein cholesterol appears to have beneficial properties on vascular function. There is increasing evidence that inflammation is also involved in the atherogenic process. Inflammation accelerates atherosclerosis and promotes thrombogenesis, and inflammatory biomarkers have been correlated with cardiovascular risk. There is now evidence that lowering low-density lipoprotein and raising high-density lipoprotein cholesterol have beneficial effects on inflammation that might contribute to the reduction in clinical cardiovascular events with currently available lipid-altering therapies. New therapeutic strategies are being designed to inhibit specific aspects of the inflammatory system that contribute to the initiation and progression of atherosclerosis.

*Curr Opin Cardiol. 2003 Jul;18(4):295-300*

### **New perspectives on the use of niacin in the treatment of lipid disorders.**

Therapy with niacin (nicotinic acid) is unique in that it improves all lipoprotein abnormalities. It significantly reduces low-density lipoprotein cholesterol, triglyceride, and lipoprotein(a) levels, while increasing high-density lipoprotein cholesterol levels. This makes niacin ideal for treating a wide variety of lipid disorders, including the metabolic syndrome, diabetes mellitus, isolated low high-density lipoprotein cholesterol, and hypertriglyceridemia. Niacin-induced changes in serum lipid levels produce significant improvements in both coronary artery disease and clinical outcomes. Niacin is currently available in 3 formulations (immediate release, extended release, and long acting), which differ significantly with respect to their safety and efficacy profiles. Immediate-release niacin is generally taken 3 times a day and is associated with adverse flushing, gastrointestinal symptoms, and elevations in blood glucose levels. Long-acting niacin can be taken once daily and is associated with significantly reduced flushing, but its metabolism increases the risk of hepatotoxic effects. Extended-release niacin, also given once daily, has an absorption rate intermediate between the other formulations and is associated with fewer flushing and gastrointestinal symptoms

without increasing hepatotoxic risk.

*Arch Intern Med.* 2004 Apr 12;164(7):697-705

### **Niacin for dyslipidemia: considerations in product selection.**

The efficacy and safety profiles of various forms of niacin for treating dyslipidemia are described. Niacin is well recognized for treating dyslipidemia in adults and has been shown to be effective in reducing coronary events. It has a broad range of effects on serum lipids and lipoproteins, including lowering total cholesterol, low-density-lipoprotein (LDL) cholesterol, and triglycerides. Niacin is the most effective lipid-modifying drug for raising high-density-lipoprotein (HDL) cholesterol levels and has been shown to lower Lp(a) lipoprotein. Niacin reduces triglycerides and very-low-density-lipoprotein and LDL cholesterol synthesis, primarily by decreasing fatty acid mobilization from adipose tissue. Niacin appears to raise HDL cholesterol by reducing hepatic apolipoprotein A-I clearance and enhancing reverse cholesterol transport. Niacin is metabolized through a conjugation or nicotinamide pathway. Standard immediate-release niacin is metabolized primarily through the conjugation pathway, which results in a high frequency of flushing. Long-acting niacin is metabolized through the nicotinamide pathway, which results in less flushing but increases the risk of hepatotoxicity. Extended-release niacin has a more balanced metabolism and causes fewer of both types of adverse effects. Improved serum lipid levels during niacin therapy have been associated with clinical and angiographic evidence of reduced coronary artery disease, especially when combined with statins. Niacin is particularly useful for managing high triglyceride and low HDL cholesterol levels as well as the lipid abnormalities associated with metabolic syndrome, including those commonly encountered in patients with diabetes. Several niacin products are available with significant differences in their safety and efficacy profiles. Health care providers must consider the differences between agents when recommending niacin for dyslipidemia treatment.

*Am J Health Syst Pharm.* 2003 May 15;60(10):995-1005

### **Vanadate improves cardiac function and myocardial energy metabolism in diabetic rat hearts.**

Vanadium mimicking the metabolic effects of insulin is known to decrease serum glucose levels and to influence glucose metabolism in diabetes mellitus. However, it is unclear whether vanadium ameliorates the metabolic disorder in diabetic hearts causing myocardial dysfunction. The purpose of this study was to assess the effects of vanadium on cardiac performance and energy metabolism in diabetic rat hearts. Four groups of Wistar rats were studied: untreated control rats (group C, n = 8), vanadate-treated rats (group V, n = 10), untreated diabetic rats (group DM, n = 9) induced by streptozotocin, and vanadate-treated diabetic rats (group DMV, n = 8). Vanadate-treated rats drank a 1.5 mM sodium orthovanadate ( $\text{Na}_3\text{VO}_4$ ) solution during a 4 week diabetic condition. Hearts were perfused with Krebs-Henseleit buffer after the diabetic duration. After the maximum left ventricular dP/dt and cardiac efficiency were calculated, the myocardial contents of ATP and creatine phosphate (P-Cr) and myocardial energy metabolism were assessed by cytosolic phosphorylation potential. Peak positive and negative dP/dt, and cardiac efficiency decreased significantly in group DM compared with group C, while there were no significant differences between groups C and DMV. The myocardial contents of ATP (micromol/g wet heart) and P-Cr (micromol/g wet heart), and cytosolic phosphorylation potential ( $M(-1)$ ) increased from 2.72 +/- 0.46, 1.45 +/- 0.58, and 3,530 +/- 1,220 in group DM to 3.88 +/- 0.76, 3.81 +/- 1.36, and 11,200 +/- 2,400 in group DMV, respectively. It is concluded that vanadium restored the production of high energy phosphates in the myocardium and improved myocardial dysfunction by regulating metabolic processes in diabetic rat hearts.

*Jpn Heart J.* 2003 Sep;44(5):745-57

## ABSTRACTS

### N-acetylcysteine

#### **Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases.**

This multicentre trial was undertaken to confirm previous results indicating that long-term treatment with oral acetylcysteine reduces the exacerbation rate in patients with chronic bronchitis. Two hundred and eighty-five patients, smokers or ex-smokers, with chronic bronchitis started a pre-trial placebo-period of 1 month. After this run-in period 259 patients were included in the trial and randomized into two parallel groups. The patients were treated in a double-blind way either with acetylcysteine 200 mg b.i.d. or placebo b.i.d. for 6 months. The trial was completed by 98 patients in the acetylcysteine group and by 105 patients in the placebo group. Initially, there were no significant differences between the groups. Twice weekly, the patients filled in a diary card concerning symptoms. The number of exacerbations was assessed from these cards and at visits 2, 4, and 6 months after institution of therapy. The exacerbation rate was significantly lower in the acetylcysteine group in which 40% of the patients remained free from exacerbations compared to 19% in the placebo group. Sick-leave due to acute exacerbation was significantly less common in the acetylcysteine group. The drug was well tolerated.

*Eur J Respir Dis.* 1983 Aug;64(6):405-15

#### **Are anti-oxidant and anti-inflammatory treatments effective in different subgroups of COPD? A hypothesis.**

The treatment of chronic obstructive pulmonary disease (COPD) with inhaled corticosteroids or anti-oxidants is still under debate and the identification of sub-groups of COPD patients who may benefit from either anti-inflammatory or anti-oxidant treatment is needed. We re-analysed data from an earlier study of inhaled beclomethasone therapy in COPD (n = 28) and asthma (n = 28) patients in order to determine patient characteristics that predict a favourable inhaled steroid treatment effect. A higher bronchodilatory response, a faster decline of FEV1 prior to the treatment period and a lower Tiffeneau index were significantly related to more beneficial treatment effects. Increased smoking tended to be related to less steroid treatment benefits, though it was not statistically significant. In this paper these findings are presented in light of the available literature on anti-inflammatory and anti-oxidant COPD treatment. On this basis the hypothesis is presented that anti-oxidant treatment might be relatively more effective among those COPD patients who respond less well to inhaled steroids (low reversibility and heavy smoking).

*Respir Med.* 1998 Nov;92(11):1259-64

#### **N-acetylcysteine: potential for AIDS therapy.**

The observations that people infected with HIV suffer not only from an inflammatory stress but also from depleted glutathione levels have led to a general hypothesis that these two are causally related, and that treatment of AIDS should include thiol-replenishment therapy. In particular, inflammatory stimulations are dependent on intracellular thiol levels, as they are potentiated at low glutathione levels (oxidative stress) and inhibited at high glutathione levels. Inflammatory stress may itself lead to decreased levels of glutathione. HIV has taken advantage of inflammatory signals to regulate its own replication; thus, the HIV infection is exacerbated by low levels of glutathione. We have shown that N-acetylcysteine can inhibit inflammatory stimulations, including that of HIV replication. Since N-acetylcysteine can replenish depleted glutathione levels in vivo, we suggest that it be used as an adjunct in the treatment of AIDS.

*Pharmacology.* 1993;46(3):121-9

#### **Significance of glutathione in lung disease and implications for therapy.**

Glutathione is a tripeptide that contains an important thiol (sulfhydryl) group within the central cysteine amino acid. Glutathione is involved in numerous vital processes where the reducing potential of the thiol is used. Several lung disorders are believed to be characterized by an increase in alveolar oxidant burden, potentially depleting alveolar and lung glutathione. Low glutathione has been linked to abnormalities in the lung surfactant system and the interaction between glutathione and antiproteases in the epithelial lining fluid of patients. Normal levels of intracellular glutathione may exert a critical negative control on the elaboration of proinflammatory cytokines. The increase of intracellular reactive oxygen species is believed to correlate with the activation of NF-kappa B, a transcription activator linked to the elaboration of several cytokines. There is now sufficient data to strongly implicate free radical injury in the genesis and maintenance of several lung disorders in humans. This information is substantial and will help the development of clinical studies examining a variety of inflammatory lung disorders.

*Am J Med Sci.* 1994 Feb;307(2):119-27

#### **Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure.**

**OBJECTIVES:** We sought to evaluate the efficacy of the antioxidant acetylcysteine in limiting the nephrotoxicity after coronary procedures. **BACKGROUND:** The increasingly frequent use of contrast-enhanced imaging for diagnosis or intervention in patients with coronary artery disease has generated concern about the avoidance of contrast-induced nephrotoxicity (CIN). Reactive oxygen species have been shown to cause CIN. **METHODS:** We prospectively studied 121 patients with chronic renal insufficiency (mean [±SD] serum creatinine concentration 2.8 ± 0.8 mg/dl) who underwent a coronary procedure. Patients were randomly assigned to receive either acetylcysteine (400 mg orally twice daily) and 0.45% saline intravenously, before and after injection of the contrast agent, or placebo and 0.45% saline. Serum creatinine and blood urea nitrogen were measured before, 48 h and 7 days after the coronary procedure. **RESULTS:** Seventeen (14%) of the 121 patients had an increase in their serum creatinine concentration of at least 0.5 mg/dl at 48 h after administration of the contrast agent: 2 (3.3%) of the 60 patients in the acetylcysteine group and 15 (24.6%) of the 61 patients in the control group ( $p < 0.001$ ). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly from 2.8 ± 0.8 to 2.5 ± 1.0 mg/dl ( $p < 0.01$ ) at 48 h after injection of the contrast medium, whereas in the control group, the mean serum creatinine concentration increased significantly from 2.8 ± 0.8 to 3.1 ± 1.0 mg/dl ( $p < 0.01$ ). **CONCLUSIONS:** Prophylactic oral administration of the antioxidant acetylcysteine, along with hydration, reduces the acute renal damage induced by a contrast agent in patients with chronic renal insufficiency undergoing a coronary procedure.

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