The Protection Conferred by Chelation Therapy in Post-MI Diabetics Might be Replicated by High-Dose Zinc Supplementation

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Abstract

The recent Trial to Assess Chelation Therapy (TACT) study, enrolling subjects who had previously experienced a myocardial infarction, has provided strong evidence that intravenous chelation therapy can markedly reduce risk for mortality and vascular events in diabetics, whereas no discernible benefit was observed in non-diabetics. It has plausibly been suggested that this reflects a role for transition metal ions – iron or copper – in the genesis of advanced glycation end products, key mediators of diabetic complications that can destabilize plaque. Since phlebotomy therapy fails to prevent vascular events in diabetics, labile copper may be the chief culprit whose removal by chelation mediated the benefit observed in TACT. Indeed, a number of recent studies report that the copper-specific orally-active chelator trientine can reduce risk for range of diabetic complications in rodents; a clinical trial with this agent demonstrated some decrease in left ventricular mass in diabetics with ventricular hypertrophy. However, in light of the current exorbitant expense of this agent, supplementation with high-dose zinc may represent a more feasible alternative. Zinc opposes the absorption and redox activity of copper via induction of the antioxidant protein metallothionein, which binds copper tightly. A great many studies demonstrate that increased expression of metallothionine decreases risk for tissue damage in diabetic rodents, and in some of these studies metallothionine expression was boosted by supplemental zinc. Zinc supplementation also modestly improves glycemic control in type 2 diabetics, and might reduce risk for diabetes by protecting pancreatic beta cells from oxidative stress. A long term study assessing the impact of supplementing diabetics with high-dose zinc, assessing risk for mortality, vascular events, and diabetic complications, may be warranted. Histidine, which readily forms complexes with copper that possess superoxide dismutase activity, also has potential for alleviating the contribution of loosely bound copper to AGE formation; moreover, in a recent clinical study, supplemental histidine improved insulin sensitivity and exerted anti-inflammatory and antioxidant effects in women with metabolic syndrome.

Chelation Therapy Decreases Vascular Events in Diabetics – A Role for AGE Reduction?

In the Trial to Assess Chelation Therapy (TACT), subjects who had previously experienced a myocardial infarction were randomized to receive intravenous EDTA or placebo solutions 40 times over approximately one year, and were followed for five years; primary endpoints assessed were death, re-infarction, stroke, coronary revascularization, or hospitalization for angina. Somewhat surprisingly, a major reduction in the primary endpoints was observed in the 633 diabetic subjects (hazard ratio 0.59, 95% CI 0.44-0.79; p<0.001), whereas no hint of benefit was observed in the non-diabetics. (Separate analysis of the diabetics had been pre-specified in the study’s protocol.) Some commentators have quite plausibly suggested that diabetics achieved selective benefit because transition metals (iron and copper) play an obligate role in the generation of advanced glycation end products (AGEs), which are thought to be key mediators of the micro- and macrovascular complications of diabetes. The redox activity of these metals, interacting with the hydrogen peroxide that is typically elevated in diabetic tissues,
engenders hydroxyl radicals, which in turn convert reversible protein-bound Amadori products to irreversible AGEs.\(^4\) It is notable that AGEs, the production of which is notably enhanced by the hyperglycemia and oxidative stress associated with diabetes, can act to destabilize plaque.\(^5\) A reasonable interpretation of the TACT results would therefore be that chelation therapy, by decreasing tissue levels of labile transition metals and thereby lessening formation of AGEs, helped to stabilize the atheromatous plaque of diabetics, decreasing risk for vascular events.

**Copper, Rather Than Iron, May be the Key Target of Chelation Therapy**

If this formulation is essentially correct, is either iron or copper the primary culprit whose removal was protective in the TACT study? A previous study may cast some light on this issue. The Iron and Atherosclerosis Study (FeAST) randomized 1277 patients with stable symptomatic peripheral arterial disease to a control group or a group receiving repeated phlebotomies.\(^6\) In treated patients who were reasonably compliant, baseline ferritin levels were reduced by approximately half, whereas these did not change in the controls. The secondary endpoints assessed during about 6 years of follow up were death plus non-fatal myocardial infarction or stroke. 473 diabetics were included in this study; among these, the secondary endpoints were observed in 34.5% of the controls, and 33.2% of those who received phlebotomies. In other words, a substantial reduction in tissue iron stores did not influence subsequent risk for vascular events in high-risk diabetics. This result renders doubtful the possibility that removal of tissue iron was largely responsible for the protection afforded diabetics in the TACT study.

What then about copper? Over the last decade, a number of studies from several groups have demonstrated that treatment of diabetic rats or humans with the copper-selective chelating agent trientine - long used in the treatment of Wilson’s disease – can exert a range of favorable effects: improving endothelium-dependent vasodilation, alleviating diabetes-associated heart failure and hypertrophy, preventing renal fibrosis and albuminuria, and decreasing AGE formation in the lens.\(^7\)-\(^16\) Clinically, in diabetic patients with left ventricular hypertrophy at baseline, a one-year course of oral trientine (600 mg twice daily) was associated with a gradual reduction in left ventricular mass, whereas no change was observed in the patients receiving placebo.\(^11\) Cooper notes that the chelatable copper stores in diabetic rats are higher than those in non-diabetic rats; he suggests that this reflects the fact that certain AGE-modified proteins can bind copper ions in such a way that they have strong redox activity.\(^14,\(^17\)-\(^19\) Other researchers have reached a similar conclusion, and have shown that the tail tendons of diabetic rats, as compared to those of non-diabetic rats, have about twice the copper content.\(^20\) Hence, the formation of AGEs may increase the level of redox-active labile copper in tissues, potentially catalyzing the formation of additional AGEs in a vicious cycle.

These findings are consistent with the proposition that copper removal was largely responsible for the benefits conferred on diabetics by chelation therapy in the TACT study, and that trientine or other copper-selective chelators may have important utility for decreasing risk for vascular events in diabetics, and likely decreasing risk for the range of diabetic complications as well. Unfortunately, though, trientine, as an orphan drug employed in the treatment of Wilson’s disease, is currently very expensive – currently over $3,000 for 30 capsules (250 mg) in the U.S.
Supplemental Zinc, via Metallothionein Induction, Prevents Diabetic Complications

What alternative strategies might be feasible? It is well known that high intakes of supplemental zinc can be employed in the treatment of Wilson’s disease (often as maintenance therapy after an initial course of trientine), owing to the fact that high-dose zinc promotes induction of the protein metallothionein.21-24 This protein, an antioxidant rich in cysteine groups, binds not only to zinc, but also copper and cadmium; in this bound form, copper and cadmium are innocuous. Zinc-mediated metallothionein induction in gastrointestinal epithelium tends to inhibit absorption of dietary copper, as metallothionein-bound copper is trapped in these cells, which subsequently are sloughed off into the intestinal lumen.25, 26 Hence, it is reasonable to propose that high-dose zinc supplementation might lessen the complications of diabetes by opposing the impact of tissue copper on AGE formation. The dose schedules of zinc that have been employed effectively in Wilson’s disease, with good tolerance – 50 mg zinc 2 or 3 times daily, or 25 mg 3 times daily27 – can be expected to achieve a notable induction of metallothionein.

There is indeed a substantial literature demonstrating that increased expression of metallothionein can be quite protective in diabetic rodents – whereas metallothionein knock out exacerbates the complications of diabetes.28, 29 In diabetic rodents, a general or tissue-specific increase in metallothionein is reported to provide protection from diabetic cardiomyopathy, nephropathy, and neuropathy – and also protects pancreatic beta cells from oxidative damage, decreasing onset of diabetes in some models.29-48 In many of these studies, transgenic strategies were used to increase metallothionein expression – but in some of them, zinc administration was employed. Zinc supplementation per se has been found to decrease pathogenic changes in the aorta, and inhibit the progression of diabetic cardiomyopathy and nephropathy.29, 32, 36, 38, 45, 46, 48-50 These studies do not clarify whether copper sequestration contributed importantly to the observed benefits – cysteine-rich metallothionein can function as a radical scavenger - but, in light of the foregoing discussion, this is a highly credible possibility.

The ability of metallothionein to protect beta cells casts an interesting light on epidemiology suggesting that relatively high dietary intakes or serum levels of zinc may confer some protection from type 2 diabetes.51, 52 Meta-analyses of controlled clinical trials examining the impact of supplemental zinc on glycemic control in diabetics concludes that such supplementation is modestly beneficial in this regard.53, 54 Unfortunately, these were relatively short term studies not designed to test the impact of supplemental zinc on risk for diabetic complications. A long term trial of high-dose zinc supplementation, in amounts sufficient to achieve a notable induction of tissue metallothionein, examining as end points mortality, vascular events, and progression of diabetic complications (nephropathy, cardiomyopathy, retinopathy, neuropathy), may be warranted in light of the growing evidence that labile copper plays a key malign role in promoting AGE formation and the many AGE-driven complications of diabetes.

It should be noted that zinc supplementation, via metallothionein induction, can also oppose the toxicity of cadmium.55-58 Increased body stores of cadmium, reflected in an increase in urinary cadmium, have been linked to increased risk for a number of pathologies, including nephropathy and atherosclerosis, key complications of diabetes.59-64 These apparent adverse effects of cadmium are observed in the general population, not just in subgroups with high occupational exposure. It therefore seems likely that high-dose zinc supplementation might also protect diabetics by lessening the impact of cadmium exposure. Unfortunately, chelation therapy is not an effective strategy for removing cadmium from the body, which
persists with a half-life of 10-30 years.\textsuperscript{60} Hence, the benefits observed in the TACT study were not likely mediated by cadmium reduction.

With respect to the safety and appropriateness of high-dose zinc supplementation, attention should be drawn to the AREDS1 study, which examined the impact of supplemental antioxidants or zinc (80 mg daily, accompanied by 2 mg of copper to prevent induction of copper deficiency) on progression of age-related macular degeneration.\textsuperscript{65} During a median follow-up of 6.5 years, total mortality in the zinc-supplemented subjects, relative to those not receiving zinc, was found to be 27\% lower (RR, 0.73; 95\% CI, 0.61-0.89). This intriguing finding, though robust, appears to have attracted little attention; it may imply that metallothionein has greater protective health potential than is commonly appreciated. However, zinc supplementation may also decrease mortality among the elderly by supporting efficient immune function and decreasing risk for infection.\textsuperscript{66, 67}

In the management of Wilson’s disease, zinc supplementation is usually employed as maintenance therapy after a course of trientine therapy has decreased body copper stores.\textsuperscript{21} If in the future trientine is approved for use in diabetes, and becomes available at a more reasonable cost that is insurance-reimbursable, a similar regimen – intermittent trientine, with zinc maintenance – might be the most effective strategy for diabetics. Although trientine may be inherently quicker and more thorough for decreasing extracellular copper levels than is zinc, metallothionein induction by zinc should provide some advantages – intracellular oxidant scavenging, cadmium detoxification – not achievable with trientine alone. Presumably, zinc could also be employed in conjunction with a course of EDTA chelation therapy, which, despite its cost and inconvenience, now has documented efficacy in diabetes.

**Alternative Copper Chelators – Focus on Histidine**

A number of agents – drugs and natural metabolites – have moderate affinity for copper, and their copper chelates have limited redox activity. Although these agents do not boost urinary loss of copper as trientine does, they have the potential to compete for the loosely bound copper affiliated with AGE-modified proteins, and hence may render this copper less pathogenic.\textsuperscript{2, 68, 69} Baynes and colleagues have noted that a number of commonly used drugs can suppress copper-catalyzed oxidation of ascorbate – a standard assay for copper’s redox activity – in low micromolar concentrations that may be clinically relevant.\textsuperscript{2, 68, 69} Of particular interest is the fact that the amino acid histidine accomplishes this with an IC\textsubscript{50} of 12 \textmu M; its derivative carnosine is even more potent in this regard (IC\textsubscript{50} = 4\textmu M).\textsuperscript{68} Remarkably, copper-histidine complexes have been reported to have superoxide dismutase activity with a rate constant similar to that of the enzyme.\textsuperscript{70, 71} And, inasmuch as histidine is an oxidant scavenger, it has been suggested that any hydroxyl radical generated by interaction of hydrogen peroxide with a Cu-II-histidine complex would likely be quenched immediately by the histidine itself.\textsuperscript{70} The fact that copper histidinate is well tolerated when administered parenterally to patients with the copper deficiency disorder Menkes’ disease tends to confirm the innocuous nature of this complex.\textsuperscript{72} It would be of interest to determine whether supplemental histidine might limit the contribution of labile copper to AGE production in diabetics.

This possibility is made all the more attractive by a report that dietary histidine exerts anti-inflammatory and antioxidant effects in diabetic mice and in women with metabolic syndrome.\textsuperscript{73, 74} In the clinical study, a randomized double-blind protocol, 2 g of histidine were administered twice daily; as compared to placebo-treated subjects, those receiving histidine achieved improved insulin sensitivity, a reduction in fat
mass, decreases in markers of oxidative stress, serum inflammatory cytokines (IL-6 and TNF-alpha), and non-esterified fatty acids, and an increase in adiponectin. In observational studies, plasma histidine correlates inversely with insulin resistance, oxidative stress, and inflammatory markers; in patients with chronic kidney disease, low plasma histidine also predicts increased mortality. The many beneficial effects of orally administered carnosine documented in animal studies may be largely attributable to derived histidine, as carnosinase rapidly degrades carnosine in plasma. Indeed, the antioxidant and acid-buffering merits of carnosine stem largely from its histidine moiety, and the purpose of carnosine synthesis in muscle fibers and neurons may be to trap a high concentration of non-protein histidine in these cells. How histidine mediates anti-inflammatory effects is unclear; copper chelation, oxidant scavenging activity, a boost in carnosine synthesis, and increased generation of histamine conceivably might play a role. Further clinical investigation of supplemental histidine is clearly warranted. Zinc histidinate may be a preferable source of zinc for supplementation in diabetics.

References


