

CORRESPONDENCE

ZINC SUPPLEMENTATION IMPROVES GLUCOSE DISPOSAL IN PATIENTS WITH CIRRHOSIS

To the Editor:

Recent attention has focused on the role of minor dietary constituents in chronic disease.¹ It is therefore of interest that zinc has been demonstrated to improve, although marginally, glucose metabolism in cases of liver cirrhosis. Marchesini et al, in a recent issue of *Metabolism*,² showed that supplementation with 136 mg of elemental zinc for a period of 60 days increases glucose disposal and effectiveness in subjects with glucose intolerance or diabetes associated with hyperinsulinemia, insulin resistance, and a degree of hepatocellular failure. The authors conclude that zinc supplementation is a relevant therapy in patients such as their study group.

While zinc is a recognized essential nutrient with some therapeutic effects, its potential toxicity has been underestimated.^{3,4} Supplements of a slightly larger magnitude than those used by Marchesini et al (150 v 136 mg, respectively) have been shown to produce gastrointestinal discomfort, particularly in individuals with a low body weight, that is, where the dose expressed as mg/kg body weight, is relatively high.⁵ The emetic effect is an acute toxic response, but a greater concern is the long-term effect on copper metabolism.³

A major action of zinc in the intestine is its ability to interact adversely with the absorption of copper,^{3,6,7} particularly when the ratio of zinc to copper is high. In the report by Marchesini et al, the intake of zinc has increased from a reported 15.5 mg/d (obtained from the diet) to 151.5 mg/d (diet plus supplement), while the intake of copper presumably remains constant, between 1 and 2 mg/d. As a consequence of the large increase in the dietary zinc to copper ratio, copper uptake will be reduced⁷ and the activities of copper metalloenzymes will be compromised.⁸⁻¹⁰ These include ceruloplasmin, the major transport protein, which also has ferroxidase activity, and superoxide dismutase (SOD),

which is a scavenger of superoxide radicals, and therefore has a role in preventing the generation of reactive radical species.

In humans and animal models, the activity of SOD is reduced as a result of the ingestion of relatively low doses of zinc, equivalent to those that are readily available as over-the-counter preparations.¹¹ The decrease in the activity of SOD is of the order of 20%¹¹ and the effect occurs rapidly.¹² The magnitude of the decrease in SOD will be moderated by the pathophysiological state of the patients and by the dietary copper intake, including that obtained from tap water, an underestimated source of dietary copper. On the other hand, the biological consequence of a reduction in SOD will be modulated by the bioavailability of other dietary or supplemented antioxidants, such as selenium and vitamins C and E.

In addition to the reduction in antioxidant status, a depletion of copper may exacerbate components of the metabolic syndrome. In isolated case reports, experimental copper deficiency has been shown to increase the plasma cholesterol concentration¹³ and reduce the clearance of glucose.¹⁴ Therefore, because of the zinc-copper antagonism, attempting to improve glucose tolerance by high-dose zinc supplements may, in the long term, defeat the purpose. Hence, the conclusions drawn by Marchesini et al need to be moderated by some of the side effects of zinc supplementation, namely, the induction of copper deficiency. These side effects cast serious doubts about the efficacy of large doses of zinc as therapeutic agents for the improved handling of glucose in all individuals, not only those reported with cirrhosis. The clinical sequelae of zinc supplements go beyond the regulation of glucose metabolism.

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REPLY

To the Editor:

We read with interest the comments of Samman on our article, which demonstrates that zinc supplementation improves glucose disposal in patients

with cirrhosis.¹ This study is part of a larger experience on zinc supplementation in cirrhosis, where other metabolic aspects were considered.² We are well aware of the possible toxicity of chronic zinc administration, but in the two studies reported so far no significant side effects were observed.