KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Zinc-Copper Imbalance - Part One

Hey, everybody. In this presentation, we're going to talk about copper and zinc, with a particular focus on the copper-to-zinc ratio.

Copper and zinc are among the most misunderstood nutrients and biomarkers on a blood chemistry panel. In this presentation, we're going to talk about the role of copper and zinc in a functional medicine workup with a particular focus on the importance of the copper-to-zinc ratio rather than viewing each marker on its own. Remember, with blood chemistry, we're looking at patterns. I have provided individual biomarker reference sheets in the blood chemistry notebook for you, and individual markers can certainly be important on their own in some cases, but the majority of the time, patterns are far more significant, and individual markers must be interpreted in the context of other markers. Copper and zinc are perhaps two of the best examples of this.

1

Serum copper and serum zinc are poor markers for dietary intake of copper and zinc.

There are a few really important things to understand about copper and zinc as biomarkers. First, dietary intake of these nutrients does not have a strong influence on their levels in the serum. For example, on a four-month trial of copper depletion in humans, blood copper levels stayed stable, while the activity of copper-dependent enzymes in the blood declined. Another study found that exposure to an additional 50 to 60 mcg of copper per kilogram of body weight per day for three months, or up to 150 mcg/kg of body weight per day for two months, resulted in no significant changes of superoxide dismutase activity in erythrocytes; of copper concentration in serum, erythrocytes, or mononuclear cells; and of serum ceruloplasmin.

Dietary copper from food is not known to cause toxicity because of the potent and redundant mechanisms that effectively control copper absorption, storage, and excretion over a wide range of dietary exposure levels, and toxic effects associated with copper in individuals not suffering from Wilson's disease are rare.

Finally, for every doubling of zinc intake, serum zinc only changes about 6 percent on average.

2

Numerous non-nutritional factors influence zinc and copper serum levels

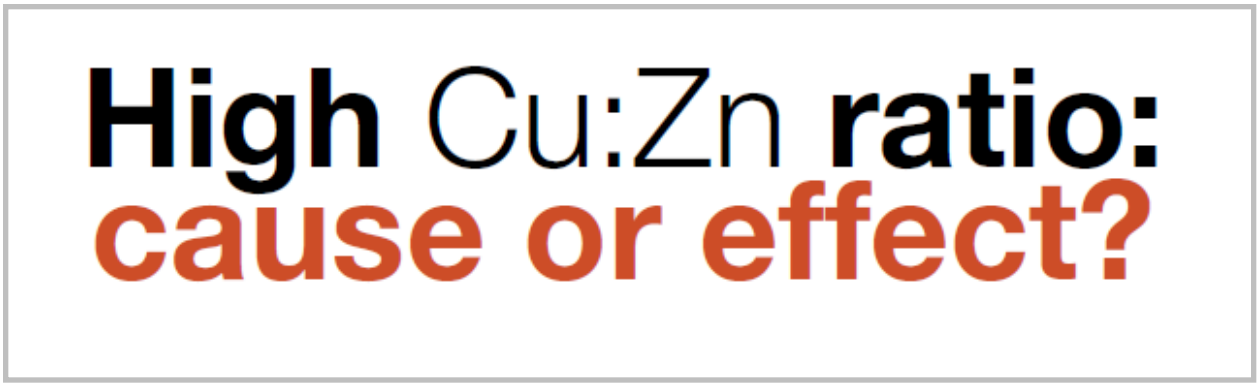
Second, and related to the points I made on the last slide, there are numerous non-nutritional factors that influence copper and zinc levels. Zinc decreases in serum during inflammatory responses and increases in liver, thymus, and bone, and this is thought to be a mechanism to restrict zinc from pathogens that require it for growth and virulence, and we'll be discussing how this also happens with iron when we talk about anemia of chronic disease in a future presentation.

It has also been shown that the albumin-bound fraction of zinc decreases in plasma, while labile zinc is loaded to peripheral tissues during some forms of oxidative stress, so that would suggest that zinc in serum goes down in oxidative stress and inflammation.

A study showed an inverse relationship between serum zinc and inflammatory markers such as interleukin-6 and CRP, but there was no inverse relationship between dietary zinc intake and those markers, which suggested that the decrease in zinc was caused by inflammation, not inadequate dietary intake.

Zinc, like cortisol, has a diurnal rhythm, so zinc levels will vary through the day, which makes accurate assessment difficult. On the other hand, copper is known to be elevated in the inflammatory response in a wide range of conditions, including aging, cardiovascular disease, malignancy, epilepsy, Alzheimer's disease, autism spectrum disorders, and increased all-cause mortality. The main copper-containing enzyme, ceruloplasmin, is an acute-phase protein and has anti-inflammatory activity. Also, the liver upregulates copper production in inflammatory states. Cytokines such as interleukin-6, interleukin-1β, tumor necrosis factor α, and interferon-gamma have been shown to suppress the synthesis of albumin, and thus the albumin-bound fraction of zinc, and to upregulate the synthesis of copper.

Finally, HPT-GA, or hypothalamic-pituitary-thyroid-gonadal-adrenal axis dysfunction, can also increase the copper-to-zinc ratio. ACTH, thyroxine, estrogens, and glucocorticoids are all well-known regulators of plasma copper levels.



In the functional medicine world, many clinicians assume high copper and low zinc are a cause of inflammation rather than a result. They also assume that zinc is low due to inadequate intake, and copper is high due to excess intake, so they will typically prescribe high doses of zinc as a treatment. I believed this myself until quite recently. The problem is, it is not supported by the research, and this approach may even be harmful. The increase in serum copper is a physiological response to inflammation rather than a promoter of it. Blood copper level correlates strongly with the marker of inflammation C-reactive protein in humans, yet substantially increasing copper intake doesn't increase CRP. This, of course, suggests that elevated blood copper is likely a symptom of inflammation rather than its cause and presents an explanation for the association between blood copper and heart attack risk.

Some studies suggest that copper deficiency worsens inflammation, even when serum copper levels are high. Furthermore, it has been shown that dietary copper must be increased to maintain adequate copper status in animals that are in an inflammatory state. Finally, prolonged use of zinc supplements may cause secondary copper deficiency, and this has been shown in several studies.

3

Serum copper and zinc do not detect mild to moderate deficiency or excess

This leads us to the third thing that you need to know, which is that currently available biomarkers for copper, especially, and to a lesser degree, zinc, are not suitable for detecting mild-to-moderate copper or zinc deficiency or excess. Serum copper levels are now considered to be rather worthless for determining copper deficiency or copper overload. The most frequently used blood markers of copper metabolism are serum copper and ceruloplasmin concentrations, and these definitely are useful to diagnose Menkes and Wilson's diseases and moderate-to-severe copper deficiency. However, these markers also act as acute-phase proteins and, as such, increase during inflammation, pregnancy, aging, and a number of diseases. Not only does high serum copper not necessarily signify copper toxicity, but copper deficiency could actually be masked when inflammation is present, similar to how ferritin elevation does not always mean iron overload and may be present even in states of iron deficiency in anemia of chronic disease, which, again, we'll be covering later on the blood chemistry unit.

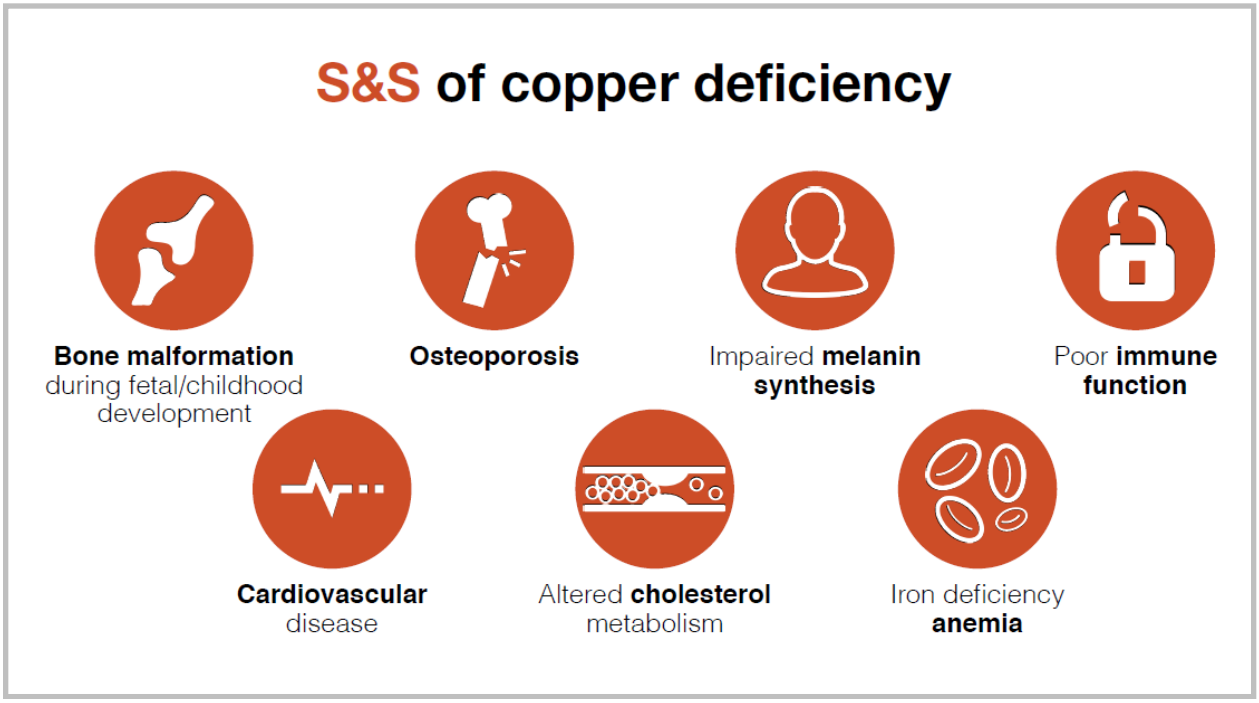
It is also clear that serum copper and ceruloplasmin are not sensitive enough to detect changes of a lesser magnitude. On the excess side, despite several efforts, currently there are no candidate diagnostic markers for detecting mild-to-moderate copper excess. In the past several years, many proteins and enzymes that are present in the blood have been measured in different conditions of copper exposure, but all of these studies have failed to identify a potential indicator of the early effects of copper excess.

Serum zinc is a little bit better than serum copper and may be the best of all available zinc biomarkers. One meta-analysis found that only serum zinc, hair zinc, and urine zinc were reliable, whereas markers such as red blood cell zinc, which many clinicians believe to be superior to serum zinc, white blood cell zinc, which is measured by labs such as SpectraCell, and then alkaline phosphatase, which is often recommended as a marker of zinc status, were not accurate indicators. This meta-analysis measured the response of these zinc markers to dietary intake and didn't consider any of the other factors that we've talked about now, such as inflammatory status and oxidative stress. Also, other studies found that serum zinc was not capable of detecting marginal zinc deficiency.

Many studies have reported positive growth response in young children who were administered zinc supplements. Elderly people are a potentially vulnerable subpopulation for zinc deficiency due to low dietary zinc intake, age-associated decreases in intestinal zinc absorption efficiency, and, probably, increases in inflammatory status and oxidative stress.

While overt zinc deficiency is rare even in vegetarians, vegetarian diets have been shown to reduce zinc absorption by up to 35 percent. Even when the diet meets or exceeds the RDA for zinc, deficiency may still occur. In fact, one study suggested that vegetarians may require up to 50 percent more zinc than omnivores for this reason.

Fourth, although there is more concern about copper toxicity than deficiency in the functional medicine world, the reality may be just the opposite. According to a 2001 study, the majority of Americans may have copper intake below the USDA recommended daily allowance and many substantially so. High intake of iron blocks the absorption of copper, causing deficiency, and chelation, or removal of iron, reverses copper deficiency. In the U.S., most people tend to eat a lot of iron-fortified refined grains and a lot of meat, which is rich in iron, yet Americans have low copper intake from both diet and water. Americans are particularly fond of muscle meat, which is rich in zinc and iron but relatively low in copper, and zinc is well known to compete with copper for absorption.



Low copper status has been associated with bone malformation during development, risk of developing osteoporosis later in life, impaired melanin synthesis, poor immune response, an increase in the frequency of infections, poor cardiovascular health, alterations in cholesterol metabolism, and iron-deficiency anemia because copper is required to move iron into and out of cells. In fact, some studies have shown that iron-deficiency anemia can be cured simply by increasing copper intake.