Trace Elements: An Association with Cardiovascular Diseases and Hypertension

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Abnormalities associated with trace elements have not received much attention from clinicians in the past; however, in the past few years there has been a veritable explosion of knowledge about trace elements which are associated with abnormalities in experimental animals as well as in humans. The information explosion is rapidly reaching the stage where clinicians will be called upon more frequently to diagnose and treat trace element-related maladies.

This article introduces to the clinician some pertinent relationships between several of the more common trace elements and their suspected relationship with cardiovascular diseases and hypertension.

Classification

Trace minerals may be classified as they relate to biological systems as essential, therapeutic, toxic, or inert.

Essential trace elements are those that are absolutely required for catalytic biochemical reactions necessary for sustaining life of the animal. Essential trace elements have been linked to their participatory role in various enzyme systems as components of enzymes, cofactors, or activators. Therapeutic trace elements are those which have applicability in the practice of the healing arts.

Toxic trace elements are classified as those which have no essential metabolic function and exert a deliteri-

ous effect directly by virtue of their presence or are antagonistic to some other essential nutrient, usually another metal.

Inert trace elements are those whose concentrations in biological systems are tolerated without a damaging effect over a very wide range of concentrations. It should be obvious that the above characterization is relative. An essential trace element may elicit responses in a living system that are damaging to the system and, hence, may be toxic. Excess concentration of essential trace elements may be toxic to biological systems. Further, the use of a mineral, such as iron as the sulfate and/or calcium as the gluconate, during pregnancy is an example of essential elements used therapeutically. Finally, in consideration of the relativeness of these categories, there is no such thing as a biologically inert element. If present in a high enough concentration, an element usually considered as inert becomes toxic.

There are at least five trace elements that may be involved in cardiovascular diseases; two are directly involved, and three may act cojointly.

Manganese and Chromium

It is generally accepted that atherosclerosis is associated with deranged metabolism of carbohydrates and lipids. Manganese and chromium are necessary for proper glucose metabolism. Manganese or chromium-deficient rats show reduced tolerance to ingested glucose.[1] Manganese is also involved in lipid metabolism. It stimulates hepatic synthesis of cholesterol and fatty acids and, hence, may be involved in regulating cholesterol levels as related to endogenous synthesis. It is a cofactor for acetyl CoA carboxylase and mevalonic kinase.[2] Both enzymes are operative in the metabolic pathway for cholesterol synthesis although the kinase is not involved in fatty acid synthesis. Manganese is widely distributed

in nature, but occurs only in trace amounts in biological materials and animal tissues. The question of manganese deficiency in humans is essentially a moot one, however, manganese toxicity, arising in workers who were exposed to manganese fumes, is not. There occurred in some of these persons a psychiatric disturbance similar to schizophrenia, which in some instances presented the clinical picture of patients afflicted with Parkinson disease, including the cardiovascular component.[3]

Chromium was recognized as an epidemiologic hazard when it was demonstrated that workers exposed to high levels of airborne chromate had an increased incidence of respiratory malignancy. The major activity of chromium, however, is considered to be an intrinsic part of the glucose tolerance factor, hence, at trace levels, it is an essential element (metal).

Chromium, in biological systems, is closely linked to insulin. Experimental chromium deficiency causes a diminution in response of insulin-sensitive tissue to the hormone.[3]

Copper

That copper has a possible role, cojointly, in the development of cardiovascular disease is supported by the fact that the element is essential for the activity of numerous plasma and connective-tissue amine oxidases. Cardiac failure associated with copper deficiency was first observed in cattle in "falling disease." Sudden death observed in these animals was believed to be due to a heart lesion which consisted of myocardial atrophy and replacement fibrosis.[4]

Using rats, Kelly et al[5] have reported heart failure in young rats whose dams consumed a copper-deficient diet. The hearts of the dams were grossly enlarged and some had aneurysms of the apex. Similar lesions have been reportedly observed in the pig.[6]

Cadmium and Zinc

A trace metal believed to be causal in cardiovascular disease is cadmium. It has been shown to be a factor in hypertension. Since cadmium and zinc are intimately related in biological systems, both must be considered. Zinc is an essential trace mineral and cadmium

is a toxic one. Cadmium is a metabolic antagonist of zinc. The toxicity of the cadmium element may be manifest due to its own presence or due to its antagonistic action on zinc. There are obviously many factors in the genesis of hypertension (endocrine, emotional, psychomatic, neural, and renal) however, there appears to be one common denominator in most cases, altered arterial reactivity.

One major group of antihypertensive drugs is composed of chelating agents. These agents act on vessels, and, because of their efficacy, it would appear that a metal or metals are in some way involved in hypertension. A study by Schroeder, using rats which were given small doses of 20 different metals in drinking water, showed that only cadmium caused hypertension.[7]

Cadmium-induced hypertension in rats has been reversed by the injection of a zinc chelate.[8] Cadmium hypertension in rats shares some common factors with moderate hypertension in humans (elevated blood pressure, increased mortality, renal arteriosclerosis, enlarged hearts, and increased severity of atherosclerosis). Human deaths from hypertension have been associated with increased levels of renal cadmium and a high ratio of cadmium to zinc. The correlation is rather convincing.[9] Human hypertensive patients have been observed to excrete 40 to 50 times as much cadmium as did a normotensive control group.[10] One of the more striking clinical effects of oral zinc is on peripheral vascular disease.[11] Doses of 150 mg per day, as the sulfate, gave improvement in the circulation of ischemic extremities and the heart. The improved circulation was not accompanied by a rise in blood pressure distal to an obstruction of an artery of a lower limb, indicating vasodilation specifically in ischemic areas. The mechanism of action may involve the displacement of cadmium from the ischemic arterial wall by zinc, when zinc is available in excess.

Blacks in America have a higher incidence of hypertension than other ethnic groups. Whether this is related to trace elements has not been studied. Morgan[11] was unable to show a difference in tissue (liver and kidney) or in the molar ratio of cadmium to zinc between patients who died with hypertension and other causes (traumatic, ischemic heart disease, and malignant disease).

Conclusions

Normal concentrations or imbalances of trace metals may influence the incidence of cardiovascular diseases, including hypertension. The involvement may be secondary to some other cause.

Experimental evidence, at least, supports the idea that chromium, manganese, zinc, cadmium, and copper are associated with cardiovascular diseases, and the role of trace metals in cardiovascular diseases, especially arteriosclerosis and hypertension, merits further study.

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