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High-dose zinc to terminate angina pectoris: A review and hypothesis for action by ICAM inhibition

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Summary We reviewed the literature related to the effects of high-dose zinc in arteriosclerosis-induced angina pectoris. Lipid peroxidation and LDL oxidation are believed to be critical for arteriosclerosis, and consequently angina pectoris. Administration of biologically available zinc was a beneficial treatment in a significant percentage of patients with severely symptomatic, inoperable atherosclerotic disease. In these patients, there was no difference in zinc concentration between patients with and without atherosclerosis in whole blood, erythrocytes or hair, but there was a major difference between normal aorta and diseased aortas (40.6 ppm zinc in normal aorta vs. 23.2 ppm zinc in atherosclerotic aorta, 40.6 ppm zinc in normal aorta vs. 19.4 ppm zinc in atherosclerotic aneurysm aorta, and no difference between normal and aneurysm aorta), although copper was low in aneurysm aorta. Medication with high-dose zinc sulfate to raise zinc serum concentrations from 95 to 177 $\mu\text{g}/\text{dl}$ resulted in objective improvement in 12 of 16 of these patients, including a patient that also had Reynard's disease. Long term environmental exposure to zinc resulted in a 40% reduction in the incidence of angina of effort compared to people not exposed to environmental zinc ($P < 0.01$) and a 40% reduction in the incidence of probable ischemia in exercise ($P < 0.001$). Lead had no effect while cadmium exposure resulted in more than tripling the incidence of angina of effort ($P < 0.001$). The antioxidative action of zinc prevents oxidation of LDL cholesterol and consequently stops the main mechanism of atherogenesis. Zinc blocks calcium and its several actions on atherogenesis. Increased amounts of cytotoxic cytokines such as $\text{TNF-}\alpha$, $\text{IL-}\beta$ and IL-8 , often produced in the elderly, are blocked by high-dose zinc. We hypothesize that higher serum concentrations of LDL cholesterol resulting from administration of 300 mg of zinc per day is caused by a release of low density cholesterol from cardiovascular tissues, beneficially flushing it into the serum where it is readily observed, thus decreasing arteriosclerosis, increasing circulation, terminating angina pectoris and restoring more youthful cardiac function. Although prevention of cholesterol-induced arteriosclerosis by zinc is predicted from findings related to oxidative stress and lipid peroxidation, removal of LDL might be attributable to action of ionic zinc on ICAM inhibition. In stark contrast to current practice, high-dose zinc should be considered as basic in the strategy of prophylaxis and therapy of the atherosclerosis process to terminate angina pectoris and restore youthful cardiac function.

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Introduction

Angina pectoris (coronary chest pain) occurs when the myocardium does not get as much oxygen as it needs usually when one or more of the heart's arteries is narrowed or blocked by low density lipoprotein (LDL) cholesterol-induced arteriosclerosis (hardening of the arteries). Lipid peroxidation and LDL oxidation are believed to be critical for arteriosclerosis. Increased amounts of cytotoxic cytokines such as TNF- α , IL- β and IL-8 are often produced in the elderly. These cytokines affect the vascular endothelium and they generate activated endothelial cell molecules, such as ICAM, VCAM and E-Selectin, etc. These molecules trap platelets, red cells, neutrophil, monocytes, etc. and plug up the blood vessels, thus producing angina pectoris. Furthermore, the monocytes—macrophages become activated and produce free radicals and reactive oxygen species (ROS) which lead to DNA oxidation and lipid peroxidation. Zinc has beneficial molecular effects in regulating these events [1].

Zinc deficiency is found in elderly hospitalized patients, and higher proportions of respiratory infections, cardiac failure, and depression were observed among zinc deficient patients as compared with the group of patients with normal zinc status [2]. Today, the elderly tend to avoid meat and other high zinc-content foods due to fears of cholesterol [3]. Rather, they increase consumption of refined wheat products. Wheat was a main source of zinc in the historical diet, but today zinc, magnesium and other critical nutrients have been depleted by the refining process [4]. Therefore, zinc deficiency may play a major, perhaps the dominant role, in causing most adverse cardiac events.

High-dose zinc (50–300 mg/day) significantly decreases serum high-density lipoprotein concentration and increases low-density lipoprotein [5–7]. while lower doses or biologically unavailable zinc compounds such as zinc oxide do not [8,9]. It is hypothesized that transient increases in low density serum cholesterol result from release of tissue bound low density lipoprotein by action of zinc. We coincidentally found that zinc could benefit angina pectoris during a zinc gluconate lozenge for common cold clinical trial.

Methods and procedures

In 1981, while conducting a clinical trial using 23 mg of zinc from zinc gluconate each 2 h to treat

common colds [10], a 65-year-old man with severe, disabling angina pectoris evaded our selection criteria and received zinc. His cold did not respond to zinc and he consumed 300 mg of zinc on the first day and 276 mg of zinc on the following days of the 7 day trial. No copper supplements were given to alter the effects of high-dose zinc.

Results

The patient returned a few days after the trial was over and wanted to know whether he had received zinc or placebo. He reported that after 5 days on zinc, his angina pectoris pain, very poorly controlled with any medication including nitroglycerin, vanished for the first time in 15 years. Indeed, his blood pressure was normal and he showed no outward evidence of coronary damage. After his zinc therapy, he went snow skiing in the mountains of Colorado for the first time in over 15 years and had no cardiac discomfort. He obtained a new job working for a railroad and felt fine working hard all day.

This effect was soon reproduced in a heavy 150 kg man with severe angina pectoris. After about a year of freedom from angina pectoris and resumption of an active lifestyle, this man's cardiologist, while remarking his great pleasure with his progress, told him to discontinue zinc because 300 mg of zinc per day would significantly decrease serum high-density lipoprotein concentration and would increase low-density lipoprotein. The patient died of congestive heart failure within a month of cessation of zinc treatment.

The observation of zinc benefit to angina pectoris was incorporated into clinical practice by one of us (WWH) but records of these results are no longer available. Nearly all persons that made dietary modifications (reduced refined carbohydrate and fat intake), stopped smoking and supplemented with 180 mg of zinc per day in split doses favorably responded to treatment. In a recent case (2005) of chronic, severe Raynaud's Disease affecting tops of both hand, face and the nose, 180 mg of zinc per day from zinc gluconate terminated Raynaud's disease within 7 days.

Discussion

There are several reports that show zinc was used to both prevent angina pectoris and effectively treat it in humans, some animal research and much biochemical and molecular biology research

showing means to prevent atherosclerosis. However, we found no insight as to how zinc might treat it.

According to a report by Henzel et al. [11] in 1968, administration of zinc sulfate was a beneficial treatment in a significant percentage of patients with severely symptomatic, inoperable atherosclerotic disease. They found that there was no difference in zinc concentration between patients with and without atherosclerosis in whole blood, erythrocytes or hair, but there was a major difference between normal aorta and diseased aortas (40.6 ppm zinc in normal aorta vs. 23.2 ppm zinc in atherosclerotic aorta, 40.6 ppm zinc in normal aorta vs. 19.4 ppm zinc in atherosclerotic aneurysm aorta and no difference between normal and aneurysm aorta), although copper was low in aneurysm aorta. They medicated with zinc sulfate to raise zinc serum concentrations from 95 to 177 $\mu\text{g}/\text{dl}$. Objective patient evaluation included treadmill walking, electrocardiography, plethysmography, and positional photography of ischemic limbs. Objective improvement was observed in 12 of their 16 patients, however, 6 of the 12 improved patients were discounted since factors such as weight loss and cessation of smoking may have contributed to improvement. One of these patients also had Reynard's disease, which promptly vanished. They suggested that zinc acts as a therapeutic pharmaceutical (rather than as a nutrient) in those patients with occlusive vascular disease who experience improvement when medicated with zinc. Underwood [12] in 1971 also reported beneficial effects of high-dose zinc in angina pectoris.

Giec et al. [13] in 1980 reported on 1000 physical workers (900 males, 100 females) aged 21–60 years with the professional exposure to zinc, lead or cadmium. They showed that environmental exposure to zinc in mines in Poland resulted in a 40% reduction in the incidence of angina of effort compared to people not exposed to environmental zinc ($P < 0.01$) and a 40% reduction in the incidence of probable ischemia in exercise ($P < 0.001$). Lead had no effect while cadmium exposure resulted in more than tripling the incidence of angina of effort ($P < 0.001$).

Ripa and Ripa [14] in 1994 argued that the antioxidative action of zinc prevents oxidation of LDL and consequently stops the main mechanism of atherogenesis. Zinc blocks calcium and its several favorable actions on atherogenesis. In stark contrast to current practice, they pointed out that zinc in suitable doses, should be considered as basic in the strategy of prophylaxis and therapy of the atherosclerosis process.

Hennig et al. [15] in 1996 pointed out that there is evidence that zinc can provide antiatherogenic properties by preventing metabolic physiologic derangements of the vascular endothelium. Because of its antioxidant and membrane-stabilizing properties, zinc appears to be crucial for the protection against cell-destabilizing agents such as polyunsaturated lipids and inflammatory cytokines. Zinc also may be antiatherogenic by interfering with signaling pathways involved in apoptosis. Certain lipids and zinc deficiency may potentiate the cytokine-mediated inflammatory response and endothelial cell dysfunction in atherosclerosis. Thus, the antiatherogenic role of zinc appears to be in its ability to inhibit oxidative stress-responsive factors involved in disruption of endothelial integrity and atherosclerosis. In 2000, Hennig et al. [16] suggested that zinc requirements of the vascular endothelium are increased during inflammatory conditions such as atherosclerosis. Clemons et al. [17] showed that age-related macular degeneration patients randomly assigned to receive zinc (80 mg zinc from zinc oxide) had lower mortality than those not taking zinc over a 6.5-year period (RR, 0.73; 95% CI, 0.61–0.89). Dietary supplements of copper or zinc both inhibited aortic atherogenesis in the cholesterol-fed rabbits [18,19].

Variant angina (Princemetal's angina) [20–22] has been shown to benefit from prompt magnesium sulfate administration, and IV magnesium sulfate terminated variant angina in one of us (GAE), who after 8 years of previous high-dose zinc treatment showed no coronary artery blockage.

Although the mechanisms by which zinc can prevent arteriosclerosis are defined, we are only left with the hypothesis that higher serum concentrations of LDL cholesterol resulting from administration of 300 mg of zinc per day results from release of LDL cholesterol from cardiovascular tissues. Zinc appears to flush LDL cholesterol, perhaps by action of ionic zinc on intracellular adhesion molecule (ICAM) inhibition, into the serum where LDL cholesterol is readily observed, thus decreasing arteriosclerosis, increasing circulation, terminating angina pectoris and restoring more youthful cardiac function. We suggest that the increase in low density lipoprotein shown by Chandra and others with administration of 300 mg of zinc per day is extremely beneficial rather than harmful as suggested by Chandra.

Caution with high-dose zinc treatment is advised for two reasons. First, 300 mg of zinc per day for 30 days suppresses primary immunity in young healthy adults [5], while 200 mg per day enhances primary immunity in old people [23]. Second, high-dose

zinc will lower copper serum concentrations [24], which might increase incidence of aneurysms. Copper (from copper chloride) treatment, starting 14 days before zinc treatment (4–6 mg copper/day) should be given to help prevent aneurysms. To further minimize side effects, treatment with high-dose zinc to terminate angina pectoris should not be given for longer than 14 days.

High-dose zinc treatment of atherosclerosis-induced angina pectoris should be studied immediately and extensively in nationally supported clinical trials of daily 300 mg zinc (from a biologically available source such as zinc gluconate, chloride, acetate, glycinate, histidinate or sulfate). Taurine (8–16 g/day in split doses), to help treat angina pectoris [25], regulate cardiac rhythm [25], eliminate extrasystoles [25] and prevent congestive heart failure [26], should also be given.

We suggest that widespread consumption of refined grains depleted of their minerals is a principal underlying cause of cardiovascular disease. We suggest that the practice of refining grain should be abolished world-wide. To eliminate angina pectoris, patients should eat whole grains, seeds and nuts, stop eating refined carbohydrates, reduce animal fat intake, stop smoking and receive high-dose zinc treatment for 14 days. Ironically, in the United States, marketing nutrients to treat, cure, diagnose and prevent diseases is essentially illegal under the overly broad Dietary Supplement Health Education Act of 1994.

The English translation of the Polish Giec article and the difficult to find Henzel article, and links to the other articles are on the Internet at <<http://coldcure.com/html/angina.html>>.

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