Original Research Article

A comparative study of trace element levels in coronary artery tissue of Coronary heart disease patients with serum levels in healthy individuals

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Abstract

Background: Cardiovascular disease/Coronary artery disease (CAD), leading cause of global morbidity and mortality covers any disease of the circulatory system. In-vivo antioxidant nutrients which include vitamin C, trace elements such as Se, Zn and Cu play a crucial role in defending against oxidant damage.

Objective: The aim of the present study was to investigate the changes occurring in the levels zinc (Zn), copper (Cu), and Selenium (Se) in coronary artery tissues of patients with CAD.

Material and methods: Coronary artery samples collected from these patients during bypass surgery from known CAD patients. These samples were analyzed for Se, Zn, and Cu; results are expressed in terms of wet weight. Normal Healthy serum Se, Zn, and Cu levels were also analyzed to compare with coronary artery samples.

Results: The levels of Zn, Cu and Se in patient's coronary artery samples were observed to be very low when compare to Zn, Cu and Se levels of healthy person's serum samples. In addition, our study showed that the levels of Zn and Cu in coronary artery samples were low when they compared to

heart tissue Zn and Cu levels from CVD patients from other studies. Whereas, Se levels in coronary artery samples in our study are same as heart tissues samples in previous other studies. Yet, there was limited/no observational studies were published to identify levels of trace element levels in coronary artery samples. Hence our present observations interpreted the levels of Zn, Cu and Se in coronary artery samples with 20 numbers of sample size only; further, higher number of samples needed to formulate the standard reference ranges of these trace elements in setting up a newer biochemical marker in correlation/interpretation of CVD/CAD.

Conclusion: The finding of our results showed that Se levels in coronary artery observed to be same as heart tissue levels from other study. The myocardial clinical manifestation seems to be due to alteration of levels of these trace elements in serum, tissue levels in patients. In our studies, however, the patients with coronary heart disease had, in general, lower concentrations of Zinc, copper in serum than the healthy controls.

Key words

Cardiovascular diseases, Trace elements, Antioxidants, Cardiomyopathies.

Introduction

Cardiovascular diseases (CVD) and Coronary artery diseases (CAD) are leading cause of morbidity and mortality in developed countries and is emerging as an epidemic in developing countries [1, 2, 3]. Traditional risk factors such as serum cholesterol, blood pressure, and smoking account for not more than 50% of CAD/CVD mortality [4]. There is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including CAD [5]. Oxidative free radicals increase the peroxidation of low density lipoprotein (LDL) thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis, though other mechanisms may exist [6]. Studies on the roles of trace elements in health and disease over the past 50 years have led to a good understanding of their mode of action and why they are essential to life [7].

Trace elements are those found in such small amounts in the living tissues, of the trace element appearing in the body, ten have been designed essential trace elements: Zinc, copper, manganese, iodine, iron, cobalt, molybdenum, tin, selenium and chromium [8]. Trace elements play an important role in the structure of proteins, enzymes and complex carbohydrates to participate in biochemical reactions. Zinc and Copper are the intensively and metabolically important trace metal for nutrients [9]. Trace element determinations in blood serum have become important to investigate their vital role in human metabolism, as well as to obtain information regarding the health status of individuals [10]. The higher or lower levels may be both a cause and effect of atherosclerosis or the result of another unknown parameter [11]. Magnesium is involved in all physiological interaction in myocardial tissue, coronary artery smooth muscle and sarcolemma conducting systems, including modulation of calcium and potassium channels and adenylate cyclase activity. A decrease in normal serum Mg level can have serious deleterious effects [12-14]. High serum copper is associated with increased cardiovascular mortality [15, 16]. Selenium, an essential trace element, is part of the enzyme glutathione peroxidase, which is involved in removal of hydrogen peroxide and lipid peroxides, thereby protecting cell membranes from oxidative damage. Researchers on animals report that selenium protects the heart against cardiotoxic elements, cardiotoxic xenobiotics

and viral infections affecting the heart [17-19]. Dietary selenium deficiency in Chinese people is associated with an endemic cardiomyopathy called "Keshan disease," which affects primarily children and women of childbearing age [20, 21]. Several clinical studies involving large populations have demonstrated that supplementing the diet with sodium selenite decreases the incidence of Keshan disease significantly [20-23]. A prospective epidemiological study done in Finland revealed the selenium concentration in serum to be inversely related to the risk of cardiovascular disease because of industrialization [24, 25]. In all these epidemiological and clinical studies, the selenium concentration in serum was the criterion for the selenium status of the controls and patients. However, it has not yet been proved conclusively that serum selenium concentrations accurately reflect the concentration of selenium in tissue levels. We therefore decided to investigate the correlation, if any, in tissue levels of selenium/zinc/copper in CAD and that of normal healthy serum subjects. We measured these trace-elements concentrations in patients with coronary heart disease who underwent bypass surgery.

Material and methods

All chemicals used in this study with highly purified material and no farther purification done.

Study setting

Samples were collected from Dept. of CTV Surgery, NMCH, Nellore. Analysis was done at Advanced Research Centre, Narayana Medical College, Nellore, Andhra Pradesh, India.

Reagents used

Selenium, copper, and zinc standards; HNO3, HClO4, and H2S04; sodium hydroxide, from Merck, Darmstadt, F.RG. as anti-foanung agent, Doubly distilled water (Milipore) (Milipore Corp., Bedford, MA), was used throughout.

Collection of samples and preparation

Heart-coronary artery samples were collected during bypass surgery, were stored frozen (-80^{0}C). The samples were stored in sterile containers with PBS buffer. Tissues obtained were washed with ultradistilled water and dried using filter paper. The samples were dried and treated with a 10 mL/L solution of 1 mol/L HNO3 in Triton X-10, homogenized in a mortar and second homogenisation done with solution containing HNO3/HClO4/H2S04 (8/2/3 by vol). The homogenate samples were kept in drying oven at 110°C for approximately 4 hours. After the samples were evaporated until they come to an appropriate dryness, they were filtered using syringe filters 0.2 micron size and completed to a volume of 1 mL using ultradistilled water.

Blood was collected from 20 healthy peoples to measure reference ranges of Zn, Cu, and Se. Blood samples collected by venipuncture; serum was collected by 10 min of centrifugation after the blood had clotted.

Sample analysis

Atomic absorption spectrophotometer method was used to determine trace element levels. Cooper, zinc, selenium were estimated by using AA-7000 Fatomic absorption spectrophotometer (SHIMADZU, Japan). Selenium levels analyzed using graphite furnace AAS method. The serum samples were also analyzed for Cu, Zn and Se levels with the stock standard solutions.

Statistical analysis

All levels of Zn, Cu and Se values were expressed in Mean and analysis done using Microsoft Excell sheet.

Results and Discussion

Coronary artery samples were taken during bypass surgery from known coronary heart disease patients. Serum from 20 healthy

individuals was also taken to compare the trace element levels with artery samples.

In present study, copper levels observed to be 0.5-1.5 in µg/g weight of coronary artery from patients with CAD. In our study, the copper levels in healthy serum samples observed to be 60-120 µg/dL. In study by O. Oster, et al., (1989) the copper levels in heart tissue levels were observed to be 1.8-5.2 µg/g tissue. In the same study, the copper levels in serum of CAD patients observed to be 39-118 µg/dL [26]. Hence, there are discriminate results observed among Cu levels in coronary artery samples from CAD, heart tissue samples from CAD and serum samples. (**Table - 1**) The levels Cu in CAD patient's coronary artery samples were observed to be very low when compared to Cu levels of healthy person's serum samples. Our study showed that the levels of Cu in coronary artery samples were showed small changes when they compared to heart tissue Cu levels in CAD patients from other studies. Kanabrocki, et al. (1964, 1965, 1967) observed a slight increase in the copper level in the serum, and a significant increase in the urine, of patients suffering from myocardial infarction [27-29]. Starting from the assumption that oxidation of serum and arterial deposit lipids may be involved in the initiation of atherosclerosis by facilitating conversion of fatty streaks into fibrous plaques, he postulated that copper, a good lipid oxidation catalyst, may play a role in this process and may enhance atherogenesis. Indeed Harman (1964, 1966, 1968) found that in experimental animals the addition of copper to the diet resulted in a higher degree of atherosclerosis and that human subjects with a history of myocardial infarction have a significantly higher serum-copper concentration (Harman, 1963) [30-33]. He also found (1965) that soft drinking-waters, whose use was repeatedly found to be associated with higher cardiovascular mortality rates (see above), have

significantly higher concentration of copper than hard waters. As a result of his findings that serum copper levels are positively correlated with coronary heart disease, Harman (1963) postulated that determinations of this metal in serum may aid in identifying coronary-prone individuals and that lowering of copper levels by dieting or chemical means may decrease the probability of development of atherosclerosis [31-34]. In atherosclerotic subjects the copper content of the aorta wall decreases [35, 36] while that of the myocardium increases [36]. It has also been reported that copper deficiency causes defective synthesis of collagen and elastin in the aorta and other blood vessels [37], thus damaging the elastic properties of the blood vessel walls. Among the cationic ligands, copper deserve particular consideration because it act as transition metal, it is very potent to generate ROS after a reaction with oxygen. Free Cu (II) ion can interact with hydrogen peroxide (H_2O_2) leading to the formation of the deleterious hydroxyl radical via the Fenton reaction. Bound to proteins, copper is generally less susceptible to participate in the Fenton reaction [38].

In present study, Zinc levels observed to be 1.5-8.5 in µg/g weight of coronary artery from patients with CAD. In our study, the Zn levels in healthy serum samples observed to be 60-120 µg/dL. In study by O. Oster, et al., (1989) the Zinc levels in heart tissue levels were observed to be 12.3-20.1 µg/g tissue. In the same study, the Zinc levels in serum of CAD patients observed to be 33-103 µg/dL [26]. Hence, there are discriminate results observed among Zn levels in coronary artery samples from CAD, heart tissue samples from CAD and serum samples. (**Table - 2**) The levels Zn in CAD patient's coronary artery samples were observed to be very low when compared to Zn levels of healthy person's serum samples. Our study showed that the levels of Zn in coronary

artery samples were showed small changes when they compared to heart tissue Zn levels in CAD patients from other studies. Carroll (1966) reported that zinc concentration in the air correlates strongly with death rates from hypertension and atherosclerosis, as cadmium does [39]. Schroeder and Buckmann (1967) found that, in rats, the administration of zinc reverses the hypertension induced by cadmium, probably because the two elements compete for the same binding sites, and that a direct relationship exists between blood pressure and molar ratios of cadmium to zinc in kidneys: when such ratio is higher than 0.35 the animal is likely to develop hypertension. This seems to be true for man also since the renal cadmium-to-zinc ratio increases with age and reaches a peak in the age-group 40-50 years [40]. As regards the relationship of zinc to atherosclerosis, a few Soviet investigators studied the behavior of this element in the aorta wall of atherosclerotic subjects. The results, however, were contradictory: some authors reported that zinc concentration in the aorta wall increases in atherosclerosis [35, 36, 41] whereas others found that it decreases [42]. Quite recently, the beneficial effect of zinc therapy in atherosclerotic patients has been reported [43]. Zinc appears to be related also to myocardial infarction. The concentration of this element decreases in the injured heart tissue [44-47]; this decrease is perhaps related to the disappearance of lactic dehydrogenase, a zinc enzyme, from the infarcted heart tissue. It decreases also in the serum of infarcted patients [48].

For all 20 patients, selenium concentrations in coronary artery showed variable ranges (**Table - 3**). In present study, selenium levels observed to be 0.15-0.45 in µg/g weight of coronary artery from patients with CAD. In our study, the Se levels in healthy serum samples observed to be 50-100 µg/dL. In study by O. Oster, et al., (1989)

the Se levels in heart tissue levels were observed to be 0.135-0.277 µg/g tissue. In the same study, the Se levels in serum of CAD patients observed to be 28-104 µg/dL [26]. The levels se in CAD patient's coronary artery samples were observed to be same when they compared to Se levels of heart tissue samples in other study. (**Table - 3**) Selenium, which is mostly bound in proteins-most probably as selenocysteine or selenomethionine- seems to be an exception. Selenium deficiency causes cardiac necrosis in mice [49] but not in rats. In dogs, on the other hand, injections of selenium in trace amounts produce cardiac damage and blood-pressure changes. Human body uses selenium to produce glutathione peroxidase, which works with vitamin E to protect cell membranes from damage caused by dangerous, naturally occurring substances known as free radicals produced by oxidative metabolism, Selenium is taking center stage as a potential anticancer agent by promoting formation of white blood cells which destroys the cancer cells and is an essential component of more than ten selenoproteins with multiple biochemical functions. Moreover, it boosts the immune system by increasing the activity and number of white blood cells and prevents premature ageing, degenerative diseases, cardiovascular diseases, inflammatory diseases, stroke, cataracts, and rheumatoid arthritis. Deficiency of the element can cause Keshan disease, characterized by an enlarged heart and poor heart function [50].

Therefore, levels of Zn, Cu and Se in patient's coronary artery samples were observed to be very low when compare to Zn, Cu and Se levels of healthy person's serum samples. The current study showed that the levels of Zn and Cu in coronary artery samples were low when they compared to heart tissue Zn and Cu levels from CVD patients from other studies. Whereas, Se levels in coronary artery samples in our study

are maximally same as heart tissues samples in previous other studies. The concentrations of zinc, copper, selenium in healthy serum show no relevant association with those in coronary artery samples in our study. This does not exclude the possibility that extreme deficiency or an overload (poisoning) of these elements could not be detected in serum or whole blood and that under these conditions also the tissue might show low or high element concentrations.

Conclusion

The finding of our results showed that Se levels in coronary artery observed to be same as heart tissue levels from other study. The myocardial clinical manifestation seems to be due to alteration of levels of these trace elements in serum, tissue levels in patients. In our studies, however, the patients with coronary heart disease had, in general, lower concentrations of Zinc, copper in serum than the healthy controls.

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Table - 1: Copper levels in µg/g weight tissue of CAD patients and healthy serum Cu levels.

Sample	Serum Cu (µg/dL) range	Heart tissue Cu concentration per gram wet weight (µg/g tissue)	Coronary artery Cu concentration per gram wet weight
Healthy control	60-120	--	--
Patients with CVD	39-118*	1.8-5.2*	0.5-1.5

*O. Oster, et al., Clinical chemistry, 1989; 35(5). [26]

Table - 2: Zinc levels in µg/g weight tissue of CAD patients and healthy serum Zn levels.

Sample	Serum Zn (µg/dL) range	Heart tissue Zn concentration per gram wet weight (µg/g tissue)	Coronary artery Zn concentration per gram wet weight
Healthy control	60-120	--	--
Patients with CVD	33-103*	12.3-20.1*	1.5-8.5

*O. Oster, et al., Clinical chemistry, 1989; 35(5). [26]

Table - 3: Serum Selenium levels µg/g weight tissue of CAD patients and healthy serum Se levels.

Sample	Serum Se (µg/L) range	Heart tissue Se concentration per gram wet weight (µg/g tissue)	Coronary artery Se concentration per gram wet
Healthy control	50-100	--	--
Patients with CVD	28-104*	0.135-0.277*	0.15-0.45

*O. Oster, et al., Clinical chemistry, 1989; 35(5). [26]