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SIGNIFICANCE OF PYRIDOXINE HYDROCHLORIDE AND COPPER IN THE PREVENTION OF ATHEROSCLEROSIS (Systematic review)

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Abstarct

Cardiovascular diseases of atherosclerotic origin are the leading cause of death in the world (Bonow et al. 2002); Incidence and mortality due to these diseases increase with urbanization and industrialization (Global Atlas on Cardiovascular Disease Prevention and Control 2011). Diseases of the cardiovascular system are the main cause of disability and mortality worldwide [O.S. Pavlova 2012]. According to many experts, this problem will continue for several decades.

INTERHEART studies have shown that 70% of primary myocardial infarction is associated with dyslipidemia.

Introduction

Vitamin B6 is an essential micronutrient and has established intakes. The recommended daily intake of pyridoxine is 2-2.5 mg/day for men, 1.8-2 mg/day for women (pregnant 2.3 mg/day, lactating 2.5 mg/day). With diet violations, stress, and various diseases, the body's need for pyridoxine increases [29]. In the human body, about 80% of vitamin B6 is found in the muscles, liver, myocardium and kidneys. Pyridoxine improves the use of unsaturated fatty acids by the body, has a beneficial effect on the functions of the nervous system, liver, hematopoiesis and CCC function. Vitamin B6 deficiency is significantly more common in patients with coronary heart disease (CHD) [28]. The formation of early atherosclerosis in the rat aorta has been associated with hyperhomocysteinemia and a decrease in antioxidant activity caused by low concentrations of vitamin B6 in vivo [N. Endo, 2007]. Vitamin B6 deficiency and absolute or relative copper deficiency are affected by a common metabolic event, namely lysyl oxidase function during connective tissue maturation, which may be of significance in the initial involvement of atherosclerosis [L.M. Klevay, 1971]. Pyridoxine contributes to the normalization of blood coagulation by eliminating lipid disorders, reducing hyperhomocysteinemia and inflammation of the endothelium. [32]. Long-term intake of B6 at a dose of 4.6 mg/day is associated with a significant reduction in the risk of developing CVD by 33% [29]. Treatment of patients with hypertension with pyridoxine preparations can significantly reduce systolic and diastolic blood pressure, levels of adrenaline and norepinephrine in blood plasma

[30]. The proven pharmacodynamic effects of pyridoxine include decongestant and antihypertensive: taking 5 mg/day of pyridoxine for 4 weeks was accompanied by a decrease in blood pressure, an increase in diuresis, loss of excess fluid, and a decrease in the tone of the sympathetic part of the autonomic nervous system [31]. The federal guidelines for the use of drugs recommend the use of pyridoxine in doses of 5–10 mg/day for all types of obliterating vascular diseases and their thrombosis [33]. In a large Danish study involving 10,601 healthy volunteers (mean age 56 years), the effects of all known B6 vitamers, folate, cobalamin, riboflavin on levels of total homocysteine, cystathionine, cysteine, methionine and creatinine were analyzed. Among the B6 vitamers, blood pyridoxal phosphate showed the strongest inverse correlation with total homocysteine and cystathionine: with an increase in pyridoxal phosphate levels, the level of homocysteine decreased [34]. The effect of pyridoxine on the neutralization of homocysteine and the elimination of chronic inflammation (including the endothelium) has been repeatedly confirmed in clinical and epidemiological studies. Plasma levels of pyridoxal phosphate and C-reactive protein (CRP) were measured in a cohort study of 1205 people aged 45–75 years. A statistically significant dose-dependent correlation was established between the levels of pyridoxal phosphate and CRP. Higher plasma pyridoxal phosphate levels were significantly consistent with lower glucose and glycated hemoglobin levels [35]. The NHANES study (National Health and Nutrition Examination Surve, an exploratory review of health and nutrition conducted by the US Centers for Disease Control) confirmed the relationship between low vitamin B6 intake and the pro-inflammatory status of patients [36]. Pyridoxine and its derivatives pyridoxal and pyridoxamine are essential for the metabolism of carbohydrates, proteins and fats [P.M.Abraham, 2010]. Pyridoxine is involved in maintaining the sodium-potassium balance and is required for the synthesis of the neurotransmitters serotonin, dopamine, norepinephrine and epinephrine. Pyridoxine plays an important role in the regulation of insulin synthesis and secretion. A number of experimental and clinical studies have shown the relationship between the availability of vitamin B6, DM and MS. [37].

It was noted that the content of pyridoxine in the liver (which is the depot of vitamin B6) in animals with diabetes model was as high as in controls [38]. Pyridoxal phosphate, supporting insulin secretion and reducing oxidative stress, contributed to the protection of the cells of the islets of Langerhans [39]. Clinical studies have confirmed the relationship between the risk of type 2 diabetes and a decrease in pyridoxine levels [40]. Observations on groups of women with gestational diabetes in late pregnancy showed that taking pyridoxine (100 mg / day) even for a relatively short period (2 weeks) contributed to a statistically significant improvement in the

glucose tolerance curve [41,42]. The effects of excess homocysteine on blood pressure are probably caused by vasoconstriction, impaired renal function and increased sodium retention, and increased arterial wall stiffness due to atherosclerotic changes. Antihomocysteine therapy, including folates and the folate synergists pyridoxine (B6) and cyanocobalamin (B12), reduces blood pressure [43]. The dietary supplement is made in the form of a tablet and contains pyridoxine hydrochloride (vitamin B6), cyanocobalamin (vitamin B12), folic acid (vitamin B9), allows you to maintain a normal level of homocysteine in the blood without causing side effects. In addition, it has a wide preventive spectrum against atherosclerosis and associated diseases [1]. Copper has been known to mankind since antiquity. Since ancient times, dishes have been made from copper. Until now, in the countries of Central Asia, wedding pilaf is cooked in a copper cauldron. This metal has not lost its significance in modern science, including medicine. Copper is used to make intrauterine devices and some surgical instruments [5]. Copper is one of ten metals, which are called "metals of life". This element is necessary for the normal functioning of the human body, on the one hand, but on the other hand, it is toxic at elevated concentrations [Chasova E.V., 2012]. Copper is part of enzymes that have redox activity and are involved in the metabolism of iron, stimulates the absorption of proteins and carbohydrates, and is involved in the processes of providing tissues of the human body with oxygen. In addition, this microelement is a cofactor for lysyl oxidase and is necessary for the intermolecular bonding of collagen and elastin. Copper is the main component of the myelin sheath, is involved in the formation of collagen, mineralization of the skeleton, the synthesis of red blood cells, the formation of skin pigments. Clinical manifestations of copper deficiency in the body are violations of the formation and function of the cardiovascular system, the skeleton, the development of connective tissue dysplasia [9].

The content of copper in the human body varies (per 100 g of dry weight) from 5 mg in the liver to 0.7 mg in the bones, in body fluids - from 100 μg (per 100 ml) in the blood to 10 μg in the cerebrospinal fluid. And the total copper in the body of an adult is about 100 mg. Copper is part of a number of enzymes - tyrosinase, cytochrome oxidase, stimulates the hematopoietic function of the bone marrow. About 90% of the copper contained in plasma is part of ceruloplasmin. In blood serum, copper is found in two fractions.

Most (92-96%) are strongly associated with blood serum proteins - a compound with α-globulins (ceruloplasmin). A small part of plasma copper is labile bound to albumins. copper is necessary for the processes of hemoglobin formation and cannot be replaced by any other element [6]. The daily requirement for copper ranges from

0.9 to 3.0 mg/day. At the same time, the physiological need for copper in adults is 1.0 mg/day, in children - from 0.5 to 1.0 mg/day. Copper sources include chocolate, cocoa, liver, nuts, seeds, mushrooms, shellfish, salmon, and spinach [14]. Copper is an essential element required for various functions. Changes in copper levels are associated with numerous pathological conditions, including chronic ischemia, atherosclerosis, and cancer. Therefore, copper homeostasis, maintained by a combination of two copper ions (Cu (+) and Cu (2+)), is crucial for health [20]. In modern folk medicine, copper is credited with many beneficial healing properties. It is believed that when applied externally, copper normalizes the general condition, normalizes blood pressure. Widely used are the wearing of copper bracelets, the application of copper plates, nickels for hypertension, the presence of bruises, etc. - [I.D. Karomatov 2012]. Anti-inflammatory, immunomodulatory, antitumor, antimicrobial properties of copper-containing substances have been identified [A.I. Islamova, 2013]. Copper stimulates the maturation of reticulocytes and their transformation into red blood cells, promotes the transfer of iron to the bone marrow and its transformation into an organically bound form. One of the private consequences of a lack of copper in the body is a violation of the utilization of iron (ferritin) and the subsequent increase in the concentration of iron in the liver. In this case, anemia develops, as well as the synthesis of phosphatides is disturbed and the activity of cytochrome oxidase decreases [11]. It has been established that under the influence of medetherapy, the secretory function of the stomach is normalized, inflammation decreases, and destructive, erosive areas disappear [13]. Furthermore, since relative or absolute copper deficiencies contribute to hypercholesterolemia, this single dietary component may link the initial and subsequent stages of atherosclerosis pathogenesis [15].

Copper (Cu) is an essential micronutrient, but excess Cu is potentially toxic. Its important propensity to cycle between the two states of oxidation determines its frequent presence as a factor in many physiological processes through Cu-containing enzymes, including mitochondrial energy production, protection against oxidative stress (via superoxide dismutase), and extracellular matrix stability (via lysyl oxidase). Since free Cu is potentially toxic, intracellular Cu is tightly controlled by Cu transporters and Cu chaperones. Recent data indicate that these Cu transport systems play an important role in the physiological responses of cardiovascular cells, including cell growth, migration, angiogenesis, and wound repair. In response to growth factors, cytokines, and hypoxia, their expression, subcellular localization, and function are tightly regulated. Cu transport systems and their regulators have also been linked to various cardiovascular pathophysiology such as hypertension, inflammation,

atherosclerosis, diabetes, cardiac hypertrophy, and cardiomyopathy. A deeper understanding of the central role of Cu transporters and Cu chaperones in cell signaling and gene expression in cardiovascular biology makes it possible to identify new therapeutic targets for cardiovascular diseases [16]. Although activation of TRPV1 cation channels by capsaicin can reduce lipid accumulation and the formation of atherosclerotic lesions, the clinical use of capsaicin has been limited by its chronic toxicity. Coupling copper sulfide (COP) nanoparticles with antibodies targeting act TRPV1 as a photothermal switch of TRPV1 signaling in vascular smooth muscle cells (VSMCs) using infrared light.

Upon irradiation, local temperature increases open the thermosensitive TRPV1 channels and induce an influx of Ca2+. An increase in intracellular Ca2+ activates autophagy and prevents foam cell formation in VSMCs treated with oxidized low density lipoproteins. Together, this suggests that KS-TRPV1 may represent a therapeutic agent to locally and temporarily attenuate atherosclerosis [17]. Oxidative modification of LDL plays an important role in the development of atherosclerosis. High-density lipoprotein (HDL) provides protection against atherosclerosis, and the antioxidant properties of paraoxonase 1 (POH1) have been proposed to contribute to this effect of HDL. Copper ion-induced LDL oxidation was reduced to 48% to purified Q192 paraoxonase 1 risk, but only 33% equivalent paraoxonase 1 activity to R192 risk. The HDL-POH1 isoenzyme Q192 caused a 65% reduction, while the HDL-POH1 isoenzyme R192 caused only a 46% reduction in LDL oxidation by copper ions. These results reflect the fact that PON1 Q and PON1 R alloys may have different protective characteristics against LDL oxidation [18]. The theory summarized here, involving Cu deficiency in the etiology and pathophysiology of CAD, explains more attributes of the disease than any other theory. Most important is the temporal relationship between increased CAD levels and reduced dietary Cu since the 1930s, along with a parallel increase in supplementation to pregnant women with Fe, a Cu antagonist. There are over eighty anatomical, chemical, and physiological similarities between Cu-deficient animals and humans with CAD. Few of these similarities have been generated by other dietary manipulations because feeding cholesterol induces Cu deficiency in animals [19]. High levels of copper and lower levels of zinc may contribute to the development of atherosclerosis and its consequences as factors in multifactorial disease. Further studies are needed to conclude whether high serum copper and zinc levels may be a risk factor for atherosclerosis [21].

Oxidation is an important pathway in the pathogenesis of coronary heart disease (CHD) through the oxidation of low-density lipoprotein (LDL) and the formation of free radicals. Copper (Cu) is an essential micronutrient for the enzymes that catalyze

LDL oxidation reactions. Therefore, assessment of Cu in atherosclerotic disease is important [22]. Cellular copper (Cu) plays an important role in angiogenesis and extracellular matrix remodeling; increased Cu in vascular smooth muscle cells has been shown to be associated with atherosclerosis and hypertension in animal experiments [23]. Copper and its main transport protein, ceruloplasmin, have been proposed to promote the development of atherosclerosis. Much of the data comes from experimental and model animal studies. Copper and mortality were not simultaneously assessed in patients undergoing coronary angiography. Elevated concentrations of copper and ceruloplasmin are independently associated with an increased risk of all-cause and cardiovascular mortality [24].

Intracellular copper causes activation of redox-sensitive transcription factors and upregulation of inflammatory mediators in endothelial cells. Copper chelation by TTM can attenuate TNFα-induced endothelial activation and hence inhibit vascular inflammation and atherosclerosis [25]. The etiological factors of atherosclerosis are endothelial activation, characterized by an upregulation of cell adhesion molecules and pro-inflammatory chemokines and cytokines, as well as the subsequent entry of monocytes into the arterial intima. Redox-active transition metal ions, such as copper and iron, may play an important role in endothelial activation by stimulating redox-sensitive cell signaling pathways [26]. It was found that the serum levels of zinc and copper were significantly lower in patients with atherosclerosis than in the control group, but there were no significant differences in serum levels of Cu and Zn between severe atherosclerosis and mild atherosclerosis [27].

The method for obtaining a complex compound of copper with pyridoxine consists in the electrolysis of an ethanol solution of pyridoxine with copper electrodes in the presence of lithium chloride at a current density of 6 to 10 mA/cm2. The technical result is a reduction in the time for obtaining a complex compound of copper with pyridoxine [17]. Among the population, hypertension is insufficiently detected and there are cases of overdiagnosis of this disease [44].

Conclusion: It can be said that the use of pyridoxine hydrochloride and copper is highly effective in preventing atherosclerosis. Fixed combinations of copper and pyridoxine in diseases associated with atherosclerosis and their prevention provide effective results.

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