EXCESSIVE CALCIUM CONSUMPTION AS A RISK FACTOR FOR CARDIOVASCULAR DISEASES

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Summary: Calcium is the most abundant mineral in the human body that participates in the construction of bones and teeth, nerve impulse transmission, intracellular signaling, hormone secretion, muscle contraction, coagulation, ensuring normal heart rhythm and physiological values of blood pressure. Excessive calcium concentration, predominantly caused by improper use of supplements, predisposes to the development of cardiovascular disease. High serum calcium induces reprogramming and differentiation of smooth muscle cells into an osteoblast-like phenotype, translocation of prohypertrophic cardiomyocyte transcription factors, compromise of diastolic relaxation of the myocardium and necrosis of its contractile girdle, stimulation of coagulation reactions, stimulation of platelet aggregation, hemodynamic changes and metabolic abnormalities. Acute intoxication with calcium supplements results in an increase in blood pressure. Chronic consumption of excessive calcium concentration predisposes to atherosclerosis and calcification of blood vessels, heart attack and stroke, hypertrophy and heart failure, and heart rhythm disorders. There is a need to strengthen the response and role of the health system in informing the public about the side effects of excessive calcium consumption, limiting the widespread prescribing of supplements, as well as a possible comprehensive reassessment of the same.
Key words: calcium, toxicity, cardiovascular system

Calcium in the human body

Calcium is the most abundant mineral in the human body (1.5-2% of total body weight, approximately 1200 g) [1,2]. About 98% of the total calcium in the body is found in the bones[1,2]. The remainder was localized in teeth (1%), body fluids, muscles, and other tissues (1%) [1,2]. In bones, calcium is present in the form of calcium-phosphate complexes, primarily hydroxyapatite, which makes up almost 40% of bone weight[2]. Bones are an easily available source of calcium (50% ionized and physiologically active calcium) [1]. It can exist in body fluids as a free calcium cation (50%), bound to proteins (albumin, globulin, calmodulin and other proteins, 40%) and other ions (calcium phosphate, calcium carbonate and calcium oxalate, 10%) [3,4]. The concentration of calcium in the serum of healthy people is in the range 8.88 - 10.4 mg / dl[4].

Calcium absorption, excretion and homeostasis

Calcium is absorbed by active transport (low and moderate levels of intake) and passive diffusion (high intake) in the small intestine[2]. Active transport is regulated by 1,25-dihydroxyvitamin D and its intestinal receptors, while passive diffusion involves movement depending on the concentration gradient[2]. Calcium absorption is inversely proportional to intake (highest in infancy and early puberty, gradually declining with age) and somewhat lower in females[2]. About 50% of plasma calcium (ionized and complex form, ultrafiltrable fraction, excluding protein-bound form) is freely filtered through the renal glomerulus, approximately 99% of which is reabsorbed along the tubule[5]. 24h adult urine contains about 200 mg of calcium[5]. During 24 h, 140 mg of calcium (a mixture of unsorbed calcium, calcium from mucosal cells and intestinal secretions) is excreted in the faeces, with sweat 35 ± 4 mg[6]. Parathyroid hormone, calcitriol (1,25-dihydroxycholecalciferol) and calcitonin7 participate in calcium homeostasis (at the level of the skeletal system, kidneys and small intestine)[6,7]. Parathyroid hormone stimulates the mobilization of calcium from the bones (stimulation of osteoclast and osteocyte activity), reabsorption of calcium in the renal tubules and the synthesis of calcitriol in the same[7]. Calcitriol increases the concentration of calcium-binding protein in the small intestine, calcitonin reduces the resorption of bone tissue (inhibition of

osteoclast activity) [7]. Calcium homeostasis may be contributed by estrogen, testosterone, adrenal hormones, thyroxine, somatotropin, and glucagon[6,7].

Recommended daily calcium intake

In newborns, it is recommended to take 400 mg of calcium per day[6]. At the age of 1–3 years 500 mg / day, at the age of 4–6 years 600 mg / day, at the age of 7–9 years 700 mg / day[6]. In adolescence (age 10–18 years) it is recommended to take 1300 mg of calcium per day, in the age of 19-65 years 1000 mg / day[6]. At the age of 65, it is recommended to take 1300 mg of calcium per day, in pregnancy and breastfeeding 1200 mg / day[6]. The recommended daily intake increases with decreasing bioavailability (in the cases of excessive consumption of foods rich in oxalic and phytic acid: spinach, sweet potatoes, rhubarb, beans, unleavened bread, raw beans, seeds, nuts, cereals), extreme physical activity and mechanical stress, excessive consumption of sodium chloride, amenorrhea, glucose intolerance and vegetarian diet[8].

Sources of calcium

Calcium intake is usually associated with the consumption of dairy products (100-180 mg of calcium in 100 g of milk and yogurt, 1 g of calcium in 100 g of hard cheese) [8]. In 100 grams of cereals there is 30 mg of calcium (enriched with 100-180 mg) [8]. Nuts and seeds (primarily almonds and sesame) are rich in calcium (250-600 mg of calcium per 100 g)[8]. 100 g of kale, broccoli and watercress contain 100-150 mg of calcium[8]. Total calcium intake from certain foods varies according to food consumption patterns in a given population (dairy products provide 72 and 58% of total calcium intake in the United States and the Netherlands, vegetables provide 46.9% of total calcium intake in China) [8].

Calcium supplements

Supplements for oral use include calcium in the form of calcium carbonate, calcium citrate, calcium gluconate, calcium lactate, and calcium phosphate[9-12]. Calcium carbonate is the most common and most cost-effective calcium supplement[9]. Calcium from this compound has an absorption similar to calcium from milk (taken with a meal, it depends on the low pH value) [9-12]. Calcium citrate can be taken without food (predominantly in people with achlorhydria, people using type 2 histamine receptor antagonists or protein pump inhibitors) [9]. It has a higher cost and lower efficacy than calcium carbonate (210 mg Ca in 1000 mg supplement) [9-12]. Calcium gluconate and calcium lactate are less concentrated forms of calcium[9]. The use of calcium phosphate is not recommended (limited number of studies) [9]. In the United States and Canada, 40% of people aged 19-65 and 70% of women over the age of 65 use calcium supplements[8].

The role of calcium in the human body

Calcium participates in the construction of bones and teeth, transmission of nerve impulses, intracellular signaling, hormonal secretion, muscle contraction, coagulation, ensuring normal heart rhythm and physiological value of blood pressure[13].

The role of calcium in the regulation of blood pressure

Calcium regulates blood pressure through vasoconstriction (changes in the concentration of intracellular calcium in vascular smooth muscle) and an increase in vascular volume[14]. It exerts its action through parathyroid hormone, vitamin D and the renin-angiotensin-aldosterone system[14]. Calcium intake is inversely proportional to the concentration of parathyroid hormone in plasma and the level of blood pressure[14]. Parathyroid hormone regulates blood pressure by increasing the concentration of free calcium in the cytosol (increased vascular reactivity, peripheral vascular resistance, reactions to the renin-angiotensin-aldosterone system and the sympathetic nervous system) and parathyroid hormone receptor type 1 (connects Gαs adenylate cyclase signaling pathways A, Gαq phospholipase C, β inositol triphosphate, intracellular calcium, protein kinase C, Gα12 / 13 phospholipase D, RhoA and signaling cascades activated by mitogenic protein kinase) [14]. Increased concentration of calcitriol modulates blood pressure by genomic (modification of transcription factors of intracellular vitamin D receptor gene expression) and non-genomic mechanisms (stimulation of L-type calcium channels by cyclic adenosine mono phosphate, signaling cascade adenylate cyclase / cyclic adenosine mono phosphate/ proteinprotein kinase A/fofolipase C / inositol phosphate and activation of the calcium transfer system) [14]. Calcium intake is inversely proportional to the activity of the renin-angiotensin-aldosterone system (low intake stimulates renin release, and consequent synthesis of angiotensin II and aldosterone) [14].

The role of calcium in the regulation of cardiac work

Normal heart function requires a sufficiently high concentration of calcium in systole and low in diastole [15,16]. Calcium is an important regulator of cardiac function that links electrical depolarization with cardiomyocyte contraction[15,16]. Intracellular increase of calcium allows the contractile threads of actin and myosin to be activated and slide next to each other, which shortens the cells and creates the power to move the blood[15,16].Depolarization caused by action potential activates calcium channels under voltage, which allows its flow through the sarcoplasmic reticulum into the cytoplasm (dyadic or triadic cleft) [15,16]. Diffusion of calcium ions initiates contraction by binding to troponin C within the myofibril[15,16]. Thanks to sequestration in the sarcoplasmic reticulum (an adenosine triphosphate-dependent enzyme process), calcium recovers to resting levels (diastole) [15,16]. Myocytes also possess sarcoplasmic calcium adenosine triphosphatase, (small contribution to calcium extrusion) [15,16]. Close connection between transverse tubules and sarcoplasmic reticulum in ventricular myocytes provide a synchronous increase in calcium during systole (which proves highly heterogeneous transition of calcium from the surface of the sarcolemma to the cell center as a consequence of chemical detubulation with formamide) [15,16]. Although without transverse tubules, the passage of calcium through atrial myocytes has similar spatial properties[15,16].

The role of calcium in coagulation

Calcium ions play an important role in the regulation of coagulation. In addition to platelet activation, they are responsible for the activation of several coagulation factors, including coagulation factor XIII (responsible for covalent cross-linking of formed fibrin clots, preventing their premature fibrinolysis). Coagulation factor XIII circulates in plasma as a heterotetrameric protransglutaminase composed of dimeric subunits of catalytic coagulation factor A and protective, regulatory subunits of coagulation factor B. Coagulation factor A is activated by a combination of calcium binding and the proteolytic cleavage of thrombin of the N-terminal 37-amino acid region[17.] In the extrinsic blood coagulation pathway, factor X is activated by a complex of tissue factor, factor VIIa, and calcium ions[18].

Reduced calcium consumption

Inadequate dietary calcium intake does not cause symptoms in the short term[18-20]. Hypocalcemia occurs as a result of medical problems or their treatment (hypoparathyroidism, renal failure, pseudohypoparathyroidism, liver failure, surgical removal of the stomach, vitamin D deficiency, hypomagnesemia, hypermagnesemia, Fanconi's syndrome, high doses of intravenous bisphosphonates, high-dose diuretics). In the long run, inadequate calcium intake causes osteopenia, osteoporosis and an increased risk of bone fractures (elderly people) [18-20].

Excessive calcium consumption

Excessive consumption of calcium supplements, also known as calcium supplementation syndrome, is a significant cause of hypercalcemia (frequency exceeded only by primary hyperparathyroidism and malignancies) [21-24]. Elevated blood calcium levels are predisposed to chronic diseases and drugs used in their treatment (thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs) [21-24]. Hypercalcemia predisposes to decreased glomerular filtration, atherosclerosis, uncontrolled hypertension, progressive cardiac dysfunction[21-24].

Excessive calcium consumption and hypertension

Excessive intake of calcium supplements causes an acute increase in serum calcium concentration, increase in blood pressure and total peripheral vascular resistance[25]. Acute hypercalcemia results in increased minute volume that rapidly progresses to a hemodynamic pattern with increased peripheral vascular resistance[25]. Increased serum calcium concentration is characterized by inappropriately high cardiac volume (absence of compensatory decrease in cardiac output caused by peripheral vasoconstriction) [25]. Hypertension occurs as a consequence of the direct effect of calcium on vascular smooth muscle cells (release of calcium from the sarcoplasmic reticulum activates calmodulin and myosin kinase, shortens myofilaments and causes vasoconstriction), while calcium-mediated increase in the release of epinephrine from the medulla of the adrenal gland contributes to its development [25]. Acute hypercalcemia is accompanied by an increase in hematocrit and a decrease in plasma volume (increased capillary filtration caused by pressure, increased sodium diuresis), unchanged activity of norepinephrine, renin, aldosterone and dopamine [25,26]. A study by a group of authors from California involving 57 subjects (7 subjects with normal renal function and 50 subjects with mild to severe renal insufficiency) found a statistically significant association between an acute increase in serum calcium and an increase in systolic and diastolic blood pressure (development or worsening of hypertension in 1 person with normal renal

function and 41 people with mild to severe renal insufficiency) [27]. The hypertensive response to increased serum calcium was more pronounced in patients with advanced renal failure (serum creatinine> 4 mg / 100 ml) [27].

Excessive calcium consumption, atherosclerosis and calcification of blood vessels

Large observational studies have found that an increase in serum calcium concentration caused by excessive consumption of supplements (1 g of calcium supplement increases the concentration of serum calcium 1.22–1.30 mmol / L), but not dietary calcium, contributes to the development of atherosclerosis and calcification of blood vessels[28-32]. Calcifications of the intima of blood vessels originate from apoptotic smooth muscle cells or matricular vesicles that are released from near the inner elastic lamina[28]. Its development is enhanced by lipid deposition and inflammation in the neointima[28]. Calcification can also occur in the medial layer (along the elastic lamellae and surrounding smooth muscle cells) [28]. High concentrations of calcium supplements induce reprogramming and differentiationof smooth muscle cells into an osteoblast-like phenotype and generates deposition of calcified matrix vesicles in the blood vessel wall[28.] In addition, calcium load reduces parathyroid hormone (increases the risk of adynamic or low bone regeneration) [28]. A study by American authors, which included 5448 adults without clinically diagnosed cardiovascular disease, found a statistically significant association between overuse of calcium supplements and calcification of coronary arteries (relative risk 1.22) [29]. A two-year study conducted in the United States, which included 5,147 people with verified changes in coronary blood vessels, found that the use of calcium supplements led to the increase in calcium deposition in them (regardless of plaque volume) [30]. A study by a group of British authors concluded that elevated calcium and phosphorus serum concentrations in hemodialysis patients increase cardiovascular risk and mortality [31]. Hypercalcemia induces loss of functional calcium receptors on the surface of vascular smooth muscle cells that directly prevent the deposition of mineral matrix in blood vessel walls [31] The use of calcimimetics in people with chronic renal failure can reduce the deposition of minerals in smooth muscle cells[31]. A study by a group of authors from Canada found that the use of calcium supplements, but not calcium in the diet, resulted in a statistically significant increase in abdominal aortic calcification[33,34]. Studies by a group of authors from Italy and Japan determined the existence of a statistically significant association between high serum calcium concentration and calcification of the infrarenal segment of the adominal aorta [35.36].

Excessive calcium consumption and myocardial infarction

Excessive calcium consumption predisposes to ectopic bone osteoid in arteries and heart valves and the development of myocardial infarction[37-42]. Studies by American authors have found that extremely high calcium intake (> 2500 mg per day) in the elderly statistically significantly increases the possibility of myocardial infarction[37]. A five-year study in New Zealand of 2,421 women aged 55 or over, with a life expectancy of more than five years, found a statistically significantly higher incidence of myocardial infarction in women who consumed 1000 mg of calcium per day (compared to placebo) [38]. An 18-year cohort study in Sweden verified elevated serum calcium values as an independent, prospective risk factor for myocardial infarction in middle-aged men (out of 2183 participants, 180 people developed a myocardial infarction with a statistically significantly higher initial serum calcium concentration than the rest). 2.37 ± 0.09 mmol/l versus 2.35 ± 0.09 mmol / l, p <0.03) [39]. A twelve-year study in the United States of 388.229 people aged 50-71 found a statistically significant association between the use of calcium supplements and the development of myocardial infarction in males (RR, 1.19; 95% CI, 1.03-1.37) [40]. The use of dietary supplements is more frequent and regular in women (achieved balance and stable calcium levels before the study) who have a milder effect of supplemental calcium compared to men (who started taking calcium supplements at old age) [40]. According to the authors, myocardial infarction does not predispose to the total load, but to sudden changes in calcium intake and serum concentration[40]. An eleven-year European prospective study of 23.980 participants found a statistically significant association between the use of calcium supplements and the development of myocardial infarction (HR = 2.39; 95% CI 1.12 to 5.12) [41]. A 10.8-year study in Sweden found that an increase in serum calcium (upper reference values) statistically significantly increased the incidence of myocardial infarction in men under the age of 50[41]. A group of American authors came to similar results43. Men who took more than 1,000 mg of calcium per day had a 20% higher risk of myocardial infarction than men who did not take the same (additional calcium intake in women was not associated with the development of myocardial infarction) [43]. The Women's Health Initiative found that calcium supplements (1000 mg / day) increased the risk of myocardial infarction in women who did not take calcium supplements before entering the study[44]

According to the same authors, excessive calcium intake from supplements produces temporary hypercalcemia associated with increased blood coagulation, vascular calcification and stiffness of the arteries predisposing to myocardial infarction [43-47].

Excessive calcium consumption, hypertrophy and heart failure

Left ventricular function is sensitive to disturbances in calcium metabolism[48]. Cardiomyocyte contraction and relaxation are largely determined by cytosomal calcium homeostasis[48]. A positive calcium balance can accelerate soft tissue and blood vessel calcification that predisposes to left ventricular damage and relaxation even without hypercalcemia[48]. Increased serum calcium is a potential trigger for translocation of prohypertrophic trencryption factors involved in the development of cardiomyocytes[48]. In addition, a permanent increase in intracellular calcium can lead to excessive activation of calcineurin (calcineurin cardiomyocytes are disorganized and markedly hypertrophic) [48]. Increased serum calcium concentration results in hemodynamic changes (increased left ventricular stroke volume) and the development of hypertension that disrupts calcium metabolism which in turn predisposes to myocardial hypertrophy[48]. Metabolic abnormalities (glucose intolerance, diabetes, central obesity, dyslipidemia, hyperuricaemia) caused by increased serum calcium concentrations also predispose to left ventricular hypertrophy[48]. An increase in serum calcium concentration results in intracellular hypercalcemia, which impairs myocardial repolarization (diastolic relaxation) and causes necrosis of its contractile girdle (excessive myofibril shrinkage and subsequent myocytolysis), which makes it an important factor in heart failure[48]. A Chinese authors' study of 833 patients with type 2 diabetes mellitus found that individuals with serum calcium values in the upper reference range had a statistically significantly higher incidence of left ventricular hypertrophy (analysis of serum calcium adjusted by albumin as a continuous variable, with an increase in serum calcium 1 mg/dl, the probability ratio for left ventricular hypertrophy is 2.400 (1,552-3,713) $p<0.001$) [48].

Excessive calcium consumption and heart rhythm disorders

Hypercalcemia is associated with cardiac arrhythmias, primarily with shortened QT interval, and only sometimes with slightly prolonged PR segment and QRS interval[50.51]. Hypercalcemia-associated hypertrophic cardiomyopathy causes transcriptional dysregulations of calcium-dependent protein kinase II or the calcineurin pathway, constitutive activation of calcium-dependent protein kinase IIδ, and consequent mutation in thick and thin strands of sarcomeres, which results in abnormal management of calcium and arrhythmogenic potential [50-52]. Decreased expression and activity of the sarcoplasmic endoplasmic reticular calcium adenosine triphosphatase gene has been demonstrated in an animal model but not in humans[52]. Hypertrophy loading and scarring contributes to the development of arrhythmia[52]. The literature describes cases of repeated ventricular arrhythmias (ventricular bigemia, monomorphic and polymorphic ventricular fibrillation) refractory to antiarrhythmic therapy, which disappeared with normalization of serum calcium values[50-53]. A study by American authors that included 871.029 participants diagnosed with atrial fibrillation found that people with elevated serum calcium concentrations had higher mortality, increased length of hospital stay, and increased total hospitalization costs compared to those who had normal calcium concentrations [54, 55].

Excessive calcium consumption and pulmonary embolism

It is thought that a high concentration of calcium in the blood as a consequence of excessive consumption of calcium supplements may play a significant role in the development of pulmonary embolism [56.57]. Hypercalcemia leads to vasoconstriction, initiates and accelerates coagulation reactions, stimulates platelet aggregation[57]. In addition, it impairs the reabsorption of sodium and water in the kidneys, while uncompensated polyuria due to nausea and anorexia predisposes to dehydration and hypercoagulable conditions[57]. Furthermore, elevated serum calcium concentrations have cytotoxic effects responsible for cellular apoptosis and thrombosis[57].

Excessive calcium consumption and stroke

Excessive calcium consumption is a significant risk factor for stroke[58]. A positive calcium balance (intake> 1400 g / day) over a long period of time promotes vascular calcification and the development of atherosclerosis[58]. A Spanish case control study involving people aged 40-89 years (2690 people with the first episode of non-fatal ischemic stroke and 19.538 controls) found a strong association between consuming high doses of calcium supplements (≥1000 mg / day) and non-fatal ischemic stroke (probability ratio 0.76; 95% CI, 0.45–1.26) [58]. An eleven-year study conducted in Sweden involving 34.670 people aged 49-83 found that excessive dietary calcium intake carried a statistically significant risk of

intracerebral hemorrhage (adjusted relative risk 2.04; 95% CI: 1.24– 3.35). [59]. A study by Australian authors found hypercalcaemia-activated arterial spasm for an etiological factor in focal neurological lesions associated with hypercalcemia[60]. A study by Korean authors found that high concentrations of albumin-adjusted calcium result in an increased incidence of mortality after acute ischemic stroke[60]. The influx of ionized calcium into neuronal cells mediated by N methyl D aspartate receptors results in ischemic death of those [61]. This is supported by the fact that the inhibition of the toxicity effectors of ionized calcium (calmodulin, aslcineurin, neuronal nitric oxide synthase) protects neurons from the toxic effects of excitatory amino acids[61]. Calcium-induced mitochondrial dysfunction also contributes to delayed neuronal death (oxidative stress and calcium accumulation in mitochondria result in swelling and release of mitochondrial contents)[61].

CONCLUSION

Excessive calcium concentration, caused by predominantlyimproper use of its supplements, predisposes to the development of cardiovascular diseases. High serum calcium induces reprogramming and differentiation of smooth muscle cells into an osteoblast-like phenotype, translocation of prohypertrophic cardiomyocyte transcription factors, compromise of diastolic relaxation of the myocardium andnecrosis of its contractile girdle, stimulation stimulation of coagulation reactions, stimulation of platelet aggregation, hemodynamic changes and metabolic abnormalities. Acute intoxication with calcium supplements results in an increase in blood pressure. Chronic consumption of excessive calcium concentration predisposes to atherosclerosis and calcification of blood vessels, heart attack and stroke, hypertrophy and heart failure, and heart rhythm disorders. There is a need to strengthen the response and role of the health system in informing the public about the side effects of excessive calcium consumption, limiting the broad prescribing of supplements, as well as possible comprehensive reassessment of the same.

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