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Calcium paradox: Consequences of calcium deficiency manifested by a wide variety of diseases

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Abstract: Calcium deficiency is a global problem, especially in the aging population. Among various nutrients, calcium is one of the few that is still deficient in industrialized countries such as Japan and many Western countries. Calcium deficiency is readily connected with osteoporosis, which is a decrease of bone calcium content. Less well known is the calcium outflow from bone that occurs to prevent decrease of blood calcium in calcium deficiency caused by the parathyroid hormone, with consequent calcium overflow into soft tissues and the intracellular compartment. Such intracellular paradoxical Ca overload as a consequence of nutritional calcium deficiency may give rise to a number of diseases common in old age: hypertension, arteriosclerosis, diabetes mellitus, neurodegenerative diseases, malignancy, and degenerative joint disease.

Key words: osteoporosis, osteoarthritis, parathyroid hormone, hypertension, arteriosclerosis

Introduction

Calcium intake is one of the few controversial problems in nutrition science. Although most nations agree on the need for greater calcium intake, adequate calcium intake for adults varies from the minimum of 600 mg/day to 1200 mg/day, with a wide range of choice up to the upper limit of 2500 mg/day, leaving the question open as to the degree of calcium deficiency. Whenever calcium intake is insufficient, the constancy of serum calcium is threatened, and parathyroid hormone is secreted to prevent hypocalcemia by stimulating bone resorption to bring calcium out of the bone and to increase intracellular free calcium in a variety of cells. Calcium distribution outside and inside the cell is unique in its vast difference in concentration (1 M outside and 10^{-4} M inside, a ratio of 10000:1), to maintain the signal transduction system. As soon as this subtle balance is disrupted by an increase of intracellular calcium, serious disturbance of cell function occurs, giving rise to various diseases [1]. Although systemic calcium deficiency is certainly expected to cause skeletal calcium deficiency or osteoporosis, the associated increase of cytosolic free calcium $[Ca]_i$ in cells of nonskeletal tissue may appear as a paradox. The concept of calcium paradox was at first introduced to explain a strange phenomenon during myocardial perfusion, myocardial damage, and necrosis in response to a calcium-containing solution following a calcium-free solution, that is, overload following deficiency [2]. Compared with osteoporosis as simple calcium deficiency disease of the bone, calcium paradox disease caused by intracellular calcium load in vascular cells, pancreatic islet cells, nerve cells, and cartilage cells, resulting in hypertension, arteriosclerosis, diabetes mellitus, neurodegenerative disease, and degenerative joint disease, is more divergent and complex and thus harder to understand in a unified concept. This review attempts to introducin this concept.

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Cardiovascular disease and hyperlipidemia

The most common cause of death in adult males all over the world is the so-called deadly quartet, consisting of hypertension, obesity, diabetes mellitus with insulin resistance, and hyperlipidemia [3,4]. These factors facilitate the occurrence of atherosclerosis, leading to fatal myocardial infarction and cerebrovascular disease. The role of calcium deficiency in the development of hypertension was first pointed out by MaCarron et al. through demonstration of low calcium but normal sodium intake in hypertensive subjects [5]. Both excessive salt intake and deficient calcium intake are important factors in the development of hypertension. Calcium stimulates sodium excretion, preventing salt retention, and sodium augments calcium excretion, causing calcium deficiency. Secondary hyperparathyroidism caused by calcium

deficiency causes a rise of $[Ca]_i$ that is frequently measured in platelets because of the ease of sampling [6]. In experimental models of hypertension, the effect of calcium deficiency augmenting the development of hypertension was shown even more clearly, probably because of the smaller number of environmental factors involved [7]. Spontaneously hypertensive rats absorb Ca from the intestine poorly and excrete Ca in urine readily, exhibiting high blood parathyroid hormone (PTH). A low calcium diet augments hypertension [8], whereas a high calcium diet inhibits the appearance of hypertension. A high blood insulin level is subsequently associated with hypertension. In insulin resistance commonly seen in adult-onset noninsulin-dependent diabetes mellitus, the serum insulin level is high because of the failure of target cells such as fat and muscle cells to respond to insulin action. Calcium deficiency and secondary hyperparathyroidism resulting from deficiency of $1,25(OH)_2$ vitamin D and resultant poor intestinal calcium absorption in experimental renal failure caused insulin resistance, and parathyroidectomy eliminated it. Increase of $[Ca]_i$ in fat and muscle cells apparently interferes with signal transduction and the response to insulin. Obesity is also known to show secondary hyperparathyroidism, probably related to calcium deficiency.

Hypertension causes overstretching and microinjury to the vascular wall; calcium accumulates in the vascular wall, facilitating platelet aggregation, macrophage migration, and endothelial proliferation, leading to atheroma formation. Lipid peroxidation, especially of LDL, increases $[Ca]_i$ and this in turn augments active oxygen production [9]. Lipid peroxide changes plasma membrane composition, thus increasing its calcium permeability. Any harm done by free radial and active oxygen is mediated by a rise of $[Ca]_i$, which is also caused by Ca deficiency, explaining the simultaneous occurrence of osteoporosis and arterial calcification [10].

Neurodegenerative diseases

Kobayashi, in Okayama, Japan, was the first to point out the role of Ca deficiency in the occurrence of cerebrovascular accident [11]. In an area supplied by calcium-rich river water, the incidence of apoplexy was lower than in another area supplied by river water poor in Ca content. Yase of Wakayama Medical College found one of the highest incidences of amyotrophic lateral sclerosis in the world in the Kii Peninsula, central Japan, associated with a very low calcium intake [12]. Dementia–Parkinsonian complex in Guam was also associated with an extremely low intake [13]. In all these diseases and also in Alzheimer's disease, which is becoming more and more prevalent with the increase of the elderly population, calcium deficiency associated with secondary hyperparathyroidism increases $[Ca]_i$ in brain cells. Glutamate-related Ca channels in nerve cells admit Ca into the cell under the influence of parathyroid hormone, physical and chemical stress, and anoxia, leading to impairment and deterioration of cell function and finally necrosis. The increase of $[Ca]_i$ in brain cells represents the final common path of brain death, which is inseparable from calcium deficiency.

Malignancy

Colon cancer has been found to occur more frequently in subjects with calcium and vitamin D deficiency [14]. Calcium may combine with fatty acids and bile acids metabolites, which would irritate intestinal mucosa and possibly otherwise exert a carcinogenic action. Increase of $[Ca]_i$ appears to promote mitotic proliferation of the cells through interaction with the cell cycle. Parathyroid hormone secreted in response to calcium deficiency may exert mitogenic action by raising $[Ca]_i$, in view of the radioprotective effect and stimulatory effect on hepatocyte regeneration. In Japan, where gastric cancer is more common than colon cancer, high calcium intake by milk consumption has been reported to decrease the incidence of gastric cancer.

Degenerative joint disease

Degenerative joint disease increases with advanced age along with osteoporosis, so that spondylosis deformans and osteoporosis represent two major causes of backache in the elderly. Osteoporosis is defined by a fall of bone mineral density (BMD) of the spine as shown by dual-energy X-ray absorptiometry (DXA), whereas spinal BMD always increases with the advance of spondylosis. For this reason, these two diseases have been thought to be incompatible, rarely occurring in the same individual. Measurement of pure trabecular bone in the distal radius points to a parallel relationship between osteoporosis and spondylosis deformans and osteoarthritis of the knee. Ca coming out of the bone in response to Ca deficiency and secondary hyperparathyroidism may enter the joint cartilage in addition to blood vessels and the brain, causing hardening, degeneration, and loss of cartilage, leading in turn to direct bone-to-bone contact, osteophyte formation, and other deformities, thus completing the picture of degenerative joint disease [15].

Nephrolithiasis

Nephrolithiasis as a calcium paradox disease was pointed out for the first time by Curhan et al., who

showed an inhibitory effect of high calcium intake on kidney stone formation [16]. It had been vaguely assumed by many clinicians that higher calcium intake facilitates formation of kidney stones through increasing urinary calcium excretion. The source of calcium in urine in massive and repeated kidney stone formation, however, is the skeleton rather than dietary calcium as seen in primary hyperparathyrodism and acute immobilization. In view of the huge calcium content in the bone, which can reach 1000 times daily calcium intake, the importance of bone calcium coming out on augmented resorption by PTH action in increasing urinary Ca excretion and kidney stone formation is readily recognized. In addition to Ca, oxalate and phosphate are also important components of the commonly seen kidney stone, and increase of calcium intake may inhibit oxalate and phosphate excretion in urine by directly binding them in the intestinal lumen, thus making them unabsorbable.

Conclusion

Calcium deficiency caused by insufficient intake and increased urinary loss is common all over the world, especially in the elderly population. In addition to causing skeletal calcium deficiency or osteoporosis, calcium deficiency paradoxically causes an increase of soft tissue and intracellular calcium through the action of PTH. A wide variety of cardiovascular, neurological, metabolic, and neoplastic diseases thus caused by calcium deficiency may be called the calcium paradox disease.

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