



# Calcium in Health and Nutrition- Role in Osteoporosis

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## A B S T R A C T

India is a calcium and vitamin D deficient nation. Domestication for food grains has led to calcium and vitamin D deficiency. Though the percapita consumption of milk has gone up India is still below the world average. Aging is associated with calcium deficiency, mostly because of the decreased biosynthesis of 1,25 (OH)<sub>2</sub> vitamin D in the kidney. Parathyroid hormone consequently increases, contributing to various diseases associated with aging such as osteoporosis or decrease of calcium in the bone, as well as hypertension, arteriosclerosis, Alzheimer's disease and osteoarthritis due to paradoxical increase of calcium in vascular walls, brain, cartilage and intracellular compartment of many kinds of cells. Mild calcium deficiency is hard to detect despite these serious consequences because of the remarkable constancy of blood calcium concentration maintained by elaborate homeostatic control. Only by successfully counteracting calcium deficiency by AAA Ca with outstanding absorbability, the phenomenon of calcium paradox becomes a recognizable reality within our reach. There is an urgent need to improve calcium from dietary and fortified sources as well as fortify milk and other products in India with vitamin D. Only then we can save Asian Indians from the ravages of the silent killers of calcium and vitamin D deficiency.

Key Words : calcium deficiency ; osteoporosis ; aging ; calcium paradox disease ; Active Absorbable Algal Calcium (AAA Ca), vitamin D deficiency.

### INTRODUCTION

Calcium (Ca) is the most abundant inorganic element in human body along with sodium. Unique characteristic of calcium distribution in vivo with astronomical concentration gradients among the skeletal, extracellular and intracellular compartments ; 100,000,000 in bone, 10,000 in blood and 1 in intracellular compartment, provides the basis for its vital role in signal transduction and cellular function. Compromise of such concentration gradients on account of Ca deficiency and secondary hyperparathyroidism leading to bone Ca loss or osteoporosis and rise of intracellular free Ca ( [Ca]<sub>i</sub>) may lead to diseases of Ca paradox such as hypertension, arteriosclerosis, Alzheimer's disease and other neuro- degenerative diseases, osteoarthritis, diabetes mellitus and malignancy.

Many calcium salts are available. Most of them the first and second generation ones are like CaCO<sub>3</sub> and CCM are poorly orally bioavailable. Active Absorbable Algal Calcium (AAA Ca) is a mixture of Active Absorbable Calcium ( AA Ca) and Heated Algal Ingredient (HAI) produced by heating cleaned oyster shell and seaweed *Cystophyllum fusiforme* submaximally under reduced pressure. The rationale for the new heated salts is now coming up.

### Ca AND Ca PARADOX

Manifestation of Ca deficiency may be seen directly as a brief hypocalcemia immediately corrected by parathyroid hormone-mediated Ca mobilization from bone and chronic Ca loss from bone or osteoporosis. Under emotional stimulation and hyperventilation, respiratory alkalosis lowers plasma ionized Ca concentration to aggravate the hypocalcemic manifestations of neuromuscular excitability . AAA Ca is quite effective in preventing such instability of plasma Ca and stabilize emotional irritability and neuromuscular hyperexcitability.

Indirect consequences of Ca deficiency is also called Ca paradox, because of the flooding of Ca in soft tissues and intracellular compartment in response to Ca deficiency, temporary hypocalcemia and PTH hypersecretion. In addition to the well-known examples of Ca paradox such as hypertension, arteriosclerosis, neurodegenerative diseases such as Alzheimer's disease and diabetes mellitus, osteoarthritis

or "chondro" porosis and chondrodegeneration is well explained by Ca flooding in the cartilage, and AAA Ca proved to be quite effective to prevent and reverse such process as described above, probably by replenishing Ca, inhibiting Ca release from bone and preventing its entrance into cartilage.

## Ca Absorption after Oral Load of AACa vs CaCO<sub>3</sub>

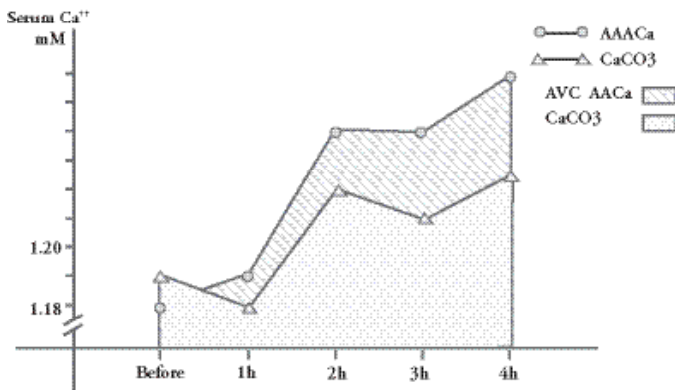


Fig. 1 Serum ionized Ca during the first 4 hours after oral ingestion of AA Ca and CaCO<sub>3</sub> to compare the absorptive efficiency. Higher ionized Ca and larger area under the curve for AACa than for CaCO<sub>3</sub> indicates higher absorption of the former than the latter.

## Delay in the Effect of Adva Cal on Vertebral Deformity from That on Vertebral Density

| Time in months                  | 3 | 6 | 9 | 12 | 18 | 24 | 27 |
|---------------------------------|---|---|---|----|----|----|----|
| Increase of Density (LBMD)      | — | + | + | +  | ++ | ++ | ++ |
| Decrease of Deformity (LBMD CD) | — | — | — | —  | ++ | ++ | ++ |

Fig. 2 Delay in the effect of AAA Ca on vertebral deformity from that on vertebral BND

Obesity, which is becoming more and more common in industrialized countries, may also represent another example of Ca Paradox. Although overnutrition is generally held responsible for overweight and adiposity, Ca deficiency may also have some contribution, through evoking emotional instability and consequent overeating and increasing [Ca]<sup>i</sup> of adipocyte leading to disruption of the control mechanism of fat metabolism. Mice with genetical activation of Ca channel develop obesity, also suggesting Ca-obesity relationship. In Katsuragi Calcium Study, whole body fat content decreased significantly in the AAA Ca Group from the Placebo Group, but not in the CaCO<sub>3</sub> Group.

Finally, kidney stone has been widely believed to be caused by Ca excess, but an extensive epidemiological study by Curhan et al) pointed out otherwise. Ca deficiency, instead of Ca excess, causes calcium Ca kidney stone, a dramatic example of Ca paradox. The best explanation for this unexpected result was provided by the binding of oxalate in the intestinal lumen by calcium, inhibiting its absorption and decreasing urinary excretion of oxalate, the presence of which precipitate Ca oxalate stones. The most reactive AAA Ca was shown to bind oxalate efficiently and

## Low Blood Ca Causes Irritation and Short Temper



Fig. 3 Low blood Ca causes irritation and short temper

## Consequence of Ca Deficiency

|                            |  |                           |
|----------------------------|--|---------------------------|
| Ca Deficiency Disease      | 1) Transient Hypocalcemia                                      | Hyperventilation Syndrome |
|                            | Neuromuscular Irritability, Emotional Instability, Convulsions | Osteoporosis              |
| Ca Paradox Disease         | 2) Bone Ca Deficiency  | Hypertension              |
|                            | 1) Increase of Ca in Blood Vessels                             | Arteriosclerosis          |
|                            | 2) Increase of Ca in Cartilage                                 | Osteoarthritis            |
|                            | 3) Increase of Ca in Brain                                     | Spondylosis deformans     |
|                            | 4) Increase of Ca in Muscles                                   | Alzheimer Disease         |
|                            | 5) Increase of Ca in Pancreas                                  | Muscular Disease          |
|                            | 6) Increase of Ca in Cytoplasm                                 | Diabetes Mellitus         |
| 7) Increase of Ca in Urine | Immune Abnormalities   |                           |
|                            |  | Malignancy                |
|                            |  | Obesity                   |
|                            |  | Kidney Stone              |

Fig. 4 Consequences of Ca deficiency

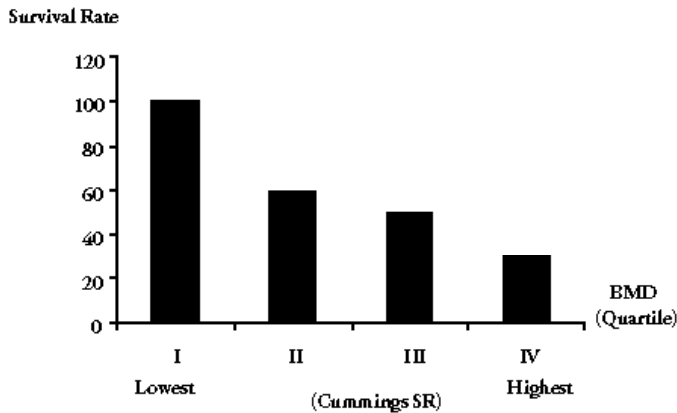
decrease urinary oxalate excretion, thereby decreasing the risk of kidney stone formation.

It is no wonder that a rise of serum PTH as the result of Ca deficiency is associated with shortening of life by giving rise to these varieties of diseases compromising normal physiological function and representing serious threats to life in a sequence of events summarized as Ca paradox (Fig 5).

## NATURE AND CHARACTERISTICS OF AAA Ca

Wasted oyster shells containing abundant Ca are abundantly found along the seacoast of Japan. In order to utilize them as a calcium supplement, oyster shells cleaned of adhering materials were heated submaximally to about 800°C under reduced pressure avoiding complete ashing to obtain active absorbable calcium (AA Ca) with a characteristic electron microscopic finding of the crystal structure: AA Ca, mainly consisting of CaO as an oxidized product of the CaCO<sub>3</sub>, is quite reactive, as expected by an extremely high electric conductivity in aqueous solution and high ionization rate. AA Ca, unlike chemically synthesized CaO or its readily transformable derivative, Ca(OH)<sub>2</sub>, is least irritable to the gastro-intestinal tract, possibly explained by its

## Blood PTH and Survival Rate



**Fig. 5** Blood PTH level and survival. Since Ca deficiency requires increased PTH secretion to release Ca from bone to restore the blood Ca level to normal, blood PTH level indicated on the horizontal axis rises in proportion to the degree of Ca deficiency. Survival rate shown as vertical bars decreases its height as blood PTH increases towards the right.

characteristic lattice-like crystalline structure, resembling the structure of the oyster shell. AACa was readily absorbed from the intestine and also an efficient phosphate binder in the intestinal lumen counteracting hyperphosphatemic state like renal failure.

By adding similarly heated seaweed *Cystophyllum fusiforme* also growing abundantly along the sea coast of Japan, Heated Algal Ingredient (HAI) to AACa, AAA Ca was produced.. AAA Ca, which was found to be even better absorbed from the intestine than AA Ca, was more efficiently absorbed than many of the known calcium preparations such as  $\text{CaCO}_3$  and calcium citrate malate, as shown by increase of urinary Ca excretion and rise of plasma ionized Ca after oral ingestion (Fig. 1). Serum parathyroid hormone (PTH) is more efficiently suppressed by AAA Ca than the same amount of Ca supplied as milk. HAI itself stimulates intestinal Ca absorption as shown by significant rise of serum Ca in rats maintained on low Ca diet for 1 week and parathyroidectomized by cautery, exhibiting hypocalcemia and low level of biosynthesis of  $1,25(\text{OH})_2$  vitamin D. The rise of serum Ca is apparently not due to an increase of bone resorption in view of the increase of bone mineral density and bone Strength Strain Index (SSI) in these animals measured by peripheral quantitative computed tomography (pQCT) measuring volumetric bone density.

### AAA Ca AND BONE

By pQCT, the only method measuring trabecular and cortical bone mineral density separately, a significant increase of trabecular bone density was demonstrated on supplementation with 900 mg AAA Ca only for 4 months, but not by supplementation with AACa,  $\text{CaCO}_3$  or placebo, in 34 pre- and postmenopausal women between 26 and 91 years of age randomly divided into 4 groups:

In a prospective, randomized, double-blind and placebo-controlled, but not by supplementation with study on 58 patients hospitalized in Katsuragi Hospital divided into 3 groups, 900

mg calcium was supplemented as AAA Ca (Group A), the same amount of calcium as  $\text{CaCO}_3$ . Group B) and placebo containing no calcium (Group C) contained in 6 indistinguishable capsules daily, in addition to hospital food containing approximately 600 mg Ca over a period of 2 years (Katsuragi Calcium Study)<sup>16,17</sup>. Lumbar bone mineral density measured by dual energy X-ray absorptiometry (DXA) significantly increased in Group A supplemented with AAA Ca than in Group C supplemented with placebo after the 6<sup>th</sup> month, but Group B supplemented with  $\text{CaCO}_3$  showed no significant difference from Group C.

New vertebral fracture occurred in 0 in Group A supplemented with AAA Ca, 143 in Group B supplemented with  $\text{CaCO}_3$  and 250 in Group C, per 1000 patient / year, with significant difference between Group A and C, but not between B and C. With advance in age, bone mineral content increased in the head, but decreased in the legs, according to our study on the distribution of the bone mineral content over the whole body by DXA. In the Katsuragi Calcium Study, head bone mineral content increased with corresponding decrease of leg bone mineral content in the placebo Group, but significantly decreased in the AAA Ca group with an increase of leg mineral content, suggesting skeletal rejuvenation. No significant change was noted in the  $\text{CaCO}_3$  Group.

Intra-individual variation of  $L_1$ - $L_4$  bone mineral density was shown to increase with advance in age along with an increase of spondylotic changes which usually starts as an increase of BMD in a single vertebra. Coefficient of lumbar spine  $L_1$ - $L_4$  BMD used as an index of intra-individual variation was found to decrease the AAA Ca Group compared to the Placebo Group from the 18<sup>th</sup> month indicating an amelioration of the spondylotic deformity (Fig. 2), but no such difference from the Placebo Group was found in the  $\text{CaCO}_3$  Group.

Attempts were made to evaluate pain in osteoporosis and osteoarthritis objectively and quantitatively by measuring a fall of skin impedance in response to exercise loading. In 80 subjects with a mean age of 65 randomly divided into 2 equal groups, A) AAA Ca-bone matrix preparation (TOKI) containing 900 mg Ca as AAA Ca, 3500 mg porcine skin collagen, 200 mg composite mucopolysaccharide and 600 mg glucosamine or B) placebo was supplemented for 4 months. Improvement of subjective pain along with significant attenuation of the fall of skin impedance was noted in response to exercise load. Basal skin impedance also increased in response to AAA Ca- matrix preparation, suggesting skin rejuvenation.

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