CALCIUM SUPPLEMENTATION: TRUTH AND MYTH

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Increased Calcium(Ca) intake (at 1.5g/day; average Indian diet <1.0g/day) has been shown to help in strengthening the bone by curtailing bone-resorbing activity (a major cause for the induction of Osteoporosis) in the elderly population (>60y, particularly females). This is indicated by the reduced levels of the sensitive bone-resorptive markers, particularly parathyroid hormone (PTH), hydroxy proline/creatinine ratio and dipyrolidine & pyrolidine/creatinine ratio. A high calcium intake is also demonstrated to reverse the secondary hyper-parathyroidism and increased bone resorption, resulting in the significant reduction in the incidence of fractures in elderly population (1,2). The normalizing influence of extra Ca-supplementation on bone-seeking radio-pharmaceutical, $^{99m}$Tc-MDP, used in the diagnosis of bone disorders; as well as Ca, modulating the propensity of $^{99m}$ Tc-Phytate uptake by bone and liver, further suggests that Ca prevents undue mobilization of bone which may otherwise lead to the onset of osteoporosis (3,4).

Due to the lack of adequate Ca in our regular Indian diet, it is necessary that we must supplement ourselves regularly with extra Ca (1.0–1.5g/d) and adequate exercise. This extra Ca-intake must not be considered as a prescribed medicine but the necessary dietary requirement like other nutrients: vegetables, fruits etc., which must be taken for the necessary maintenance of our good health.

However, there has been a strong misconception, even in the medical fraternity, that extra Ca-intake leads to formation of kidney stones. In fact, it is the extra Ca, which would help in preventing stone formation by chelating oxalates/citrates (main culprits) present in our food, to insoluble complexes, which are then excreted from the GI tract. Here, it is important to understand that only 20–30% out of ~1000mg/d of Ca ingested, gets absorbed and the rest is utilized for reacting with the unwanted products of the digestive process like oxalates, citrates, bile salts, fatty acids forming insoluble complexes, which are then excreted out in the faeces. Inadequacy of dietary Ca will allow the soluble oxalates and citrates present in our food to escape from getting complexed with Ca in the gut. They are transported to the kidneys by the blood and get insolubilized there with Ca. (Ca comes to kidney during its normal metabolic pathway where most of it is reabsorbed). The insoluble Ca oxalates/citrates deposit in the kidney and form the nucleus on which further deposition of Ca oxalates/citrates takes place over a period of time to form kidney-stones (5).

Colon cancer in the susceptible individuals could also be viewed as an unfortunate consequence of inadequate dietary Ca. On high Ca-diet, ~76-80 % of the ingested Ca remains unabsorbed in the intestinal lumen where it forms insoluble complexes with bile acids and unmetabolized fatty acids, thus sparing colonic mucosal membrane of unnecessary irritation due to these compounds. The insoluble complexes of these compounds with Ca are excreted. In normal course, to completely complex the irritant-residues from fats in a typical diet, one would require unabsorbed Ca of ~600–800mg/day – a value requiring an ingested Ca of at least ~1200mg/day. In fact, in quite a few cases of colon cancer, Ca is reported to being used successfully as a chemo-preventive agent to control the proliferation of colon cancer. In most
of these cell lines, $[^3H]$-thymidine–uptake, an indicator of cellular proliferation, is lowered in the presence of Ca (5).

An inverse association between dietary Ca intake and blood pressure is seen in many adults. The hypertensive subjects had significantly lower serum levels of ionized Ca. In another study, it has been noted that the subjects consuming high Ca diet had lowered systolic pressure. In one of the animal experiments, it was observed that rats maintained on lower Ca-diet for 7 weeks, compared to controls, had reduced gain in their body weight and raised blood pressure, consequent to reduction in the circulating levels of Ca. This could be reversed by putting these rats back to normal Ca-diet (5,8).

In another set of experiments, a group of rats rendered hypocalcemic due to Vitamin D deficiency, were found to have reduced intestinal Ca-transport and retarded growth. Laboratory tests showed that these hypocalcemic rats had altered hepatic function, raised levels of the hepatic enzymes and decreased plasma protein synthesis, and histopathology of the liver was suggestive of periportal necrosis (6). Hypocalcemia also resulted in the significant reduction of hepatic antioxidant enzymes – Super Oxide Dismutase (SOD) and Glutathione Peroxidase (GP), which are responsible for scavenging the free radicals, while lipid peroxidation was enhanced. Extra Ca-supplementation to these hypocalcemic animals, could normalize most of the parameters of the liver function as well as both the important antioxidant enzymes (SOD & GP). This is due to the influence of Ca on the stability and maintenance of Vitamin E, Glutathione & Protein–thiols, the major players in scavenging free radicals (7). These observations clearly indicate the ubiquitous nature of Ca, which is also important for many other cellular and intracellular functions besides its effect on bone strength (8).

Reduced Ca-intake evokes the response for Ca-conservation through the interplay of the Calcitropic hormone axis: Parathyroid hormone-Vitamin D-Calcitonin. When this is inadequate, Ca deficiency results. The hormone axis controls the hierarchy of regulation–levels, mentioned below (8):

1. Body Ca, i.e. skeleton, is at the bottom of this hierarchy and most vulnerable to the state of Ca-deficiency.
2. Next is the concentration of Ca in the Extra Cellular Fluid (ECF), which is a well governed area of Parathyroid hormone – Vitamin D endocrine system. It is because the ECF-Ca must be conserved even at the expense of bone that bone is at the first level to be sacrificed.
3. The third level is at the boundary between the ECF and the interior of the cell.
4. Analogous boundary also exists between intra cellular Ca–concentrating membranes and the cytosol where Ca–channels and other transport systems are operative.
5. Last, and apparently most tightly conserved Ca, is at the molecular level where Ca is bound to calmodulin and other proteins present in the cell and vascular membranes.

However, the clinical manifestations of the cellular dysfunction related to impaired cellular Ca metabolism would exhibit several features as mentioned below:

1. First - the emergence of the clinical disorders would occur in later life, as multiple compensatory mechanisms gradually fail over protracted periods of time.
2. Second - the disorders, that would develop might be anticipated to reflect the hierarchy of cell function, i.e., disorders related to cell division and growth or energy metabolism should pre-dominate.
3. Third - since multiple cell types would be affected over time, there may be strong concordance of multiple medical disorders.

This is clear from the fact that as the age advances, the degree of Ca-deficiency gradually increases more due to inadequate intake of Ca.
coupled with the reduced Ca-absorption. This leads to increased secretion of PTH, and consequently, the bone loses Ca due to increased bone resorption, leading to the debilitating bone-disease, osteoporosis. This is seen to be associated with the rise in the vascular Ca due to the blunting of the Ca-concentration gradient, increasing the chances of arteriosclerosis. All this would also depend upon the contribution of the genetic influences and environmental factors, which would exhibit differing sensitivities to the exposure to Ca-deficiency (8).

There are several chronic disorders linked to the inadequate Ca-intake, which we need to be informed about. Besides osteoporosis, the inability of the cells to regulate their own growth and replication could contribute to the development of both cancer and cardiovascular diseases resulting from the vascular hypertrophy and the change in the peripheral resistance. Several systemic metabolic disorders may be initiated due to lack of adequate Ca, affecting normal cellular metabolism. This impairment could contribute to the development of the hyperlipidemic state (5,8).

Influence on the cell membrane integrity, interfering with the Ca dependent transduction of the hormone receptor-signal, would impair the normal target organ response to hormonal action such as failure of insulin to regulate normal cellular glucose uptake, as in type-II diabetes. In this regard, lower bone mineral density (BMD) and blunted response of PTH and Calcitriol to hypocalcemia has been noted in diabetes (5,8).

All this boils down to the fact that adequate Ca-intake is a must for the maintenance of our normal health, right from the young age, failing which it could lead to various deficiency disorders. This provides us an important food for thought to reassess our dietary habits with regard to our Ca-intake. It is true that agricultural revolution has caused substantial modifications in our dietary habits and the mother nature has been kind enough, trying its level best to adjust and reorient our body to the altered environmental conditions. However, the natural adaptation of the cellular milieu seems to be still inadequate to maintain proper balance. It must be appreciated that agricultural revolution is a relatively recent event on the time scale of evolution and it is highly likely that human genome would not have sufficient time to adapt fully to a change of this magnitude due to rapid industrialization. In this regard, if we compare our dietary intake with that of our fore-fathers who were hunters and gatherers, it has been noted that their diets were rich in fiber, protein, vitamin C and particularly Ca - estimated to be 4–5 times more than what is available from our present Indian diet - which is rich in salt and fat but hardly provides 300 – 500mg Ca/day, when minimum requirement of Ca is 1g/d. Even, NIH/WHO consensus has recommended our Ca-intake must be raised from 1g/d to 1.5 to 2.4g/d, depending upon the age and physiological conditions (9,10).

### CLINICAL FEATURES OBSERVED IN HYPOCALCEMIA

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<tr>
<th>HYPOCALCEMIA</th>
<th>CLINICAL SYMPTOMS</th>
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<td>MILDE</td>
<td>No symptoms or tingling and numbness in the fingers and toes. Chvostek’s sign if provoked.</td>
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<tr>
<td>MODERATE</td>
<td>Both Chvostek &amp; Trousseau’s signs, more on provocation.</td>
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<td>SEVERE / ACUTE</td>
<td>Above symptoms plus possibility of Laryngospasm, Bronchospasm and seizures.</td>
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<tr>
<td>CHRONIC</td>
<td>Papiledema and basal ganglia – calcification, besides cataract, dry skin, coarse hair, brittle nails and defective dentition.</td>
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All this emphasizes the need for all of us to engage in more intensive dialogue with general public at large to educate them and increase their awareness about the serious implications of the inadequate intake of Ca, so that it becomes easy to embark on the road to recovery from the onslaught of many debilitating/chronic diseases. It is advisable to start Ca-supplementation from the early age, more during pregnancy/lactation periods and better to take Ca on empty stomach for its better absorption.

References


