ABSTRACT

Calcium is an essential nutrient for human beings. Calcium plays a vital role in optimal performance of a host of physiological functions. Along with vitamin D it plays a key role in maintaining bone health. However, there is compelling evidence that either of the nutrients is causally related to extra-skeletal health outcomes or that intakes greater than those recommended have benefits for health. On the contrary, there is evidence that certain population groups especially postmenopausal women may be taking calcium supplements in excess of the tolerable upper intake level, which puts them at risk of developing nephrolithiasis and perhaps unknown cardiovascular effects.

INTRODUCTION

Calcium is a mineral needed by human body for optimal bone health and physiological functioning. Calcium cannot be made from environmentally available raw materials, thus it an essential nutrient for us.

Free or ionized calcium acts as a vital second messenger in important bodily functions like blood coagulation, hormone secretion & action, muscle contraction and nerve function.

Calcium in the form of crystalline hydroxyapatite- \( \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \) - confers strength and resilience to the skeleton. Approximately 99% of total body calcium is located in the bones and teeth. The skeleton serves as calcium nutrient reserve. Nonbone calcium accounts for <1% of total body calcium. It comprises free ions (51%), protein-bound complexes (40%) and ion complexes (9%). The ionized fraction is responsible for a wide range of essential functions, including extra- and intracellular signalling, nerve impulse transmission, and muscle contraction. To avoid calcium toxicity, the concentration of serum ionized calcium is tightly maintained at 4.4 to 5.4 mg/dl.\(^1\) Parathyroid hormone (PTH) and its receptor (PTHR), 1,25 DHCC and vitamin D receptor (VDR) along with serum ionized calcium and the calcium-sensing receptor (CaR) act in tandem to maintain calcium homeostasis.\(^2\)

Dairy products, green vegetables (broccoli, bhindi, cabbage etc.), legumes, nuts (almond, walnut, hazel nut etc) and fortified foods are the major sources of dietary calcium.

INTESTINAL CALCIUM ABSORPTION

Intestinal absorption of ingested calcium involves both active (transcellular) and passive (paracellular) mechanisms. Passive calcium absorption generally ranges between 10 to 15% of intake and it is unsaturable.\(^3\) Active calcium transport occurs mainly in the proximal small intestine. This process is under the control of 1,25 dihydroxycholecalciferol (1,25DHCC). Calcium is transported across the brush border of intestinal epithelial cells via channels known as transient receptor potential vanilloid type 6 (TRPV6) and binds to an intracellular protein calbindin-D\(_{9k}\). Calbindin-D\(_{9k}\) sequesters the absorbed calcium so that it does not disturb epithelial signalling processes that involve calcium.\(^2\) The absorbed calcium is eventually transported to the antiluminal surface of the intestinal epithelial cells, from where it is transported into the blood stream by either a sodium/calcium exchanger (NCX1) or a calcium-dependent ATPase. One, twenty-five DHCC regulates this transport process by stimulating the expression of a number of gene products (TRPV6, calbindin--D\(_{9k}\), Ca\(^{2+}\)-ATPase etc.) involved in
calcium transport and handling in response to a fall in serum ionized calcium level. 2

A person needs vitamin D to ensure optimal net extraction of calcium from the digestate. For example, in the absence of active transport (in the face of vitamin D deficiency), a person would need daily calcium intake of 3000 mg for net absorption to reach 200 mg/d, which is the amount needed to offset 200 mg daily obligatory calcium loss from cutaneous and renal routes. 3 There is a plateau relation of intestinal calcium absorption fraction to vitamin D status so that the absorption efficiency rises in a linear fashion up to a serum 25, hydroxycholecalciferol (25OHCC) concentrations of 32 ng/ml, beyond which additional increases in vitamin D status are without any effect on absorption efficiency. 4

Though vitamin D is the major hormonal determinant of intestinal calcium absorption, the bioavailability of calcium may be affected by a number of local factors and dietary constituents. Absorption of calcium is impaired by bile salt deficiency, unabsorbed free fatty acids in malabsorption states, and high dietary content of fibre or phytate (as in chapatti). Administration of calcium salts with meals, use of divided doses and use of more soluble salts like calcium citrate are some of the strategies that can be employed to increase calcium bioavailability.

IS THERE NEED FOR CALCIUM SUPPLEMENTATION?

Calcium is an essential element for growth. But the requirement for calcium remains high even after growth has been completed. This is because obligatory calcium losses from the adult human body are relatively high and calcium absorption efficiency is low. Hence, adequate dietary calcium intake remains important throughout life. The dietary calcium density of contemporary diet has gone down to 40 mg/100 kcal from that of our hunter-gatherer ancestors, in whom it was 300 mg/100 kcal. 5 Modern lifestyle favouring indoor living has resulted in inadequate exposure to sunlight. 6 These factors have resulted in a pandemic of calcium and vitamin D deficiency.

There is a large body of evidence that demonstrates that both calcium and vitamin D are vital for protecting bone health. These two nutrients need each other for several of their actions on the skeleton. In evaluating evidence relating to their efficacy, it is important that they be considered together. There is unequivocal evidence that supplementing calcium and vitamin D enhances bone gain during adolescence and early adulthood and reduces age-related bone loss. By doing so they reduce fragility fractures not only in the elderly, but, also in adolescents. 7

Calcium and vitamin D maintain bone health by two mechanisms - 1) by offsetting obligatory calcium losses from the body and 2) by reducing excessive bone remodeling. 4 The primary role of calcium intake in the adult is to offset daily losses through excreta, sweat, and shed skin, nails, and hair. Excretory conservation for calcium is weak and when excretion exceeds absorbed input, the skeleton is torn down (by increasing parathyroid hormone secretion) to scavenge its calcium. Adequate calcium intake preserves the skeletal mass. Without vitamin D, only 10 to 15% of dietary calcium is absorbed. Vitamin D sufficiency enhances calcium absorption by 30-40 percent. 8 Bone remodeling has traditionally been viewed as osteoprotective, because it replaces damaged bone with fresh new bone. In perimenopausal period bone remodeling doubles and it triples by the age of 65 years. 4 The rise in remodeling after midlife appears to be driven by hormonal changes and nutritional factors rather than by any real need to repair bone. Excessive remodeling increases bone fragility. Both increased calcium intake and increased vitamin D status reduce bone remodeling by reducing parathyroid hormone secretion. In the absence of vitamin D more than 3000 mg daily calcium intake would be needed to achieve this effect. Optimum vitamin D status achieves the same effect with more typical calcium intakes.

The Institute of Medicine (IOM) first developed dietary reference intakes (DRI) for calcium and vitamin D in 1997. These values are used by the government agencies for school meals or specifying the nutrition label on foods. They are also used by health professionals to counsel individuals about dietary intake. The latest report released on November 30, 2010 is based on the evidence for the role of these nutrients on bone health but not on other health conditions. 9 These recommendations are in the form of recommended dietary allowance (RDA). RDA intends to meet the need of nearly all people. For calcium the RDA for adolescents is 1300 mg/d, for adults ages 19 through 50 it is 1000 mg/d, for women over 50 and for both men and women 71 and older it is 1200 mg/d. 9 Tolerable upper intake level (UL) for calcium is 2000 mg/d, while it is 3000 mg/d for adolescents.

Indians have lower bone mass compared to Caucasians. Majority of Indians consume diet which is low in calcium content. Vitamin D deficiency is widespread in India despite the availability of abundant sunshine. Although genetic factors account for lower bone mass, vitamin D and calcium deficiency in our population plays a crucial role by way of lower peak bone mass attained during puberty. 10 National Institute of Nutrition in its latest guideline recommends 800 mg/d of calcium for adolescents, 1200 mg/d for pregnant and lactating mothers and 600 mg/d for adult men and women. 11

ARE THERE ANY EXTRASKELETAL EFFECTS OF CALCIUM?

There are several observational studies demonstrating association between low vitamin D and calcium intake
(especially 25-OHCC below 20 ng/ml) and increased risk of several nonskeletal outcomes namely cancer, cardiovascular disease, diabetes, and autoimmune disease. The IOM committee in its report published in 2011 did not find any convincing evidence from randomized controlled trials to establish any cause-and-effect relationship between vitamin D and calcium intake and reduction in the any of the above-mentioned nonskeletal outcomes.

THE CURRENT MEDIA HYPE AND ITS FALL OUT

Over the last 10-15 years, there has been increasing interest in the possibility of a role of vitamin D and calcium in pathogenesis of a wide range of medical conditions which include cancer, autoimmune diseases, infections, type 2 diabetes and the metabolic syndrome, hypertension, and cardiovascular disease. A number of papers have been presented by researchers in medical conferences in this regard and they have attracted widespread media attention. This rapid dissemination of medical information has resulted in a situation where medical practice and patient behaviour are getting ahead of science and the concept of “more is better” is fast getting a firm foothold in the society. At a laboratory in Canada, the number of physician-ordered vitamin D tests increased from 20,000 in 2007 to more than 160,000 in 2010. In the United States, the sales of vitamin D have increased 10-fold over the last 8 years from $40 million in 2001 to $425 million in 2009.

There is evidence that calcium intake in the form of supplement is exceeding the tolerable upper limit of normal in postmenopausal women. It puts them at risk of nephrolithiasis. Bolland and his colleagues in a recent meta-analysis have shown that calcium supplement in excess of 500 mg/d without coadministered vitamin D is associated with approximately 30% increase in the risk of myocardial infarction. The same group has done re-analysis of Women’s Health Initiative data and have shown that women allocated to calcium-vitamin D administration who were not taking personal calcium supplements were at increased risk of cardiovascular events. A large population based prospective observational study was done in Sweden involving more than 60,000 women aged 53 years and above followed up for 19 years. The women in whom dietary calcium intake was below 700 mg/d had increased risk of hip fracture, any fracture, and of osteoporosis. Higher levels of calcium intake did not further decrease the rate of fracture, on the contrary, there was evidence for increased risk of hip fractures with high calcium intake.

There has been resurgence of milk-alkali syndrome over the last 15 to 20 years. Cases have been described mainly in women who do not have a history of peptic ulcer disease and have been taking calcium supplement (mainly as calcium carbonate) in excess of 1200 mg to 1500 mg per day for the prevention and treatment of osteoporosis. Furthermore, calcium has been added to many over-the-counter products and supplements, such as fast-acting antacids, vitamin preparations, juices, and even paracetamol and aspirin tablets, which have provided multiple opportunities for inadvertent excessive intake of calcium by consumers.

Due to the recent media hype over the widespread prevalence of vitamin D deficiency and many extraskeletal health advantages of vitamin D supplementation, there has been multifold rise in sale of vitamin D-containing supplements in drug stores, health food stores, and over the Internet. This has exposed consumers to the danger of vitamin D intoxication and cases of vitamin D intoxication are being increasingly reported in medical literature.

To prevent abuse of calcium it is important for clinicians to properly counsel their patients on calcium and vitamin D intake. The target group should be postmenopausal women. It is important to stress that their total calcium intake (diet plus supplements) should not exceed 1200mg per day. This issue should be reviewed with patients because some may assume that they need to take 1200 mg daily of supplements in addition to what they may be taking in their diet, leading to possibly excessive levels of calcium intake.

Clinicians need to consider milk-alkali syndrome and vitamin D intoxication in the differential diagnosis of their patients presenting with hypercalcemia.

REFERENCES:


