



Review On Calcium Intake And Its Signaling Mechanism

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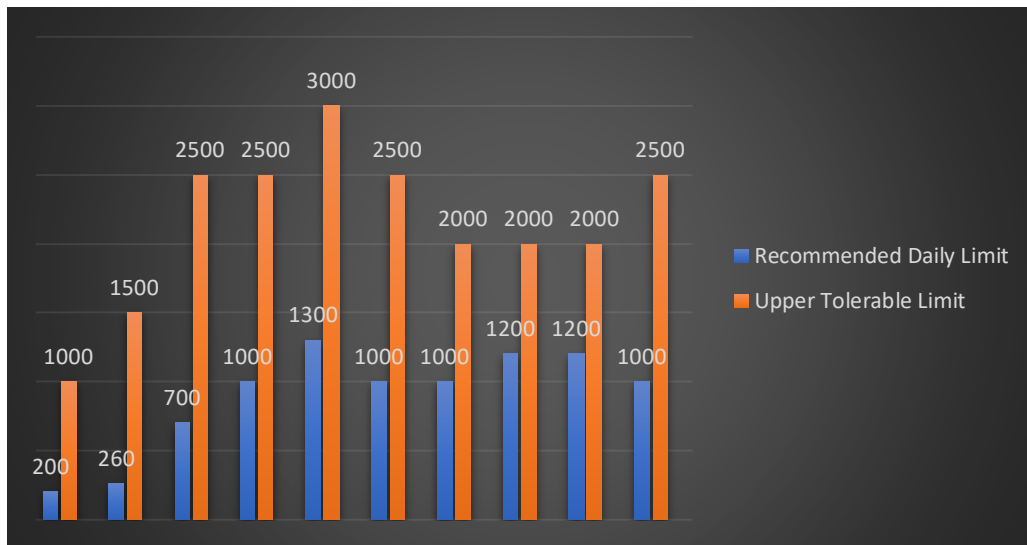


Introduction-

For health point of view an sufficient calcium intake is necessary for obtaining and maintaining supportable bone mineral density and for regulation of body wight. It may also produce protection against high blood pressure and certain type of cancer.The human body contains about 1kg of calcium with more than 99% store in bone in the form of calcium phosphate.

Calcium as a nutrient is most commonly associated with the formation and metabolism of bone. Over 99 percent of total body calcium is found as calcium hydroxyapatite in bones and teeth, where it provides hard tissue with its strength. Calcium in the circulatory system, extracellular fluid, muscle, and other tissues is critical for mediating vascular contraction and vasodilatation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion. Bone tissue serves as a reservoir for and source of calcium for these critical metabolic needs through the process of bone reworking.

Calcium metabolism is regulated in large part by the parathyroid hormone (PTH)–vitamin D endocrine system, which is characterized by a series of homeostatic feedback loops. The rapid release of mineral from the bone is essential to maintain adequate levels of ionized calcium in serum. During vitamin D deficiency states, bone metabolism is significantly affected as a result of reduced active calcium absorption. This leads to increased PTH secretion as the calcium sensing receptor in the parathyroid gland senses changes in circulating ionic calcium. Increased PTH levels induce enzyme activity in the kidney, which converts vitamin D to its active hormonal form, calcitriol. In turn, calcitriol stimulates enhanced calcium absorption from the gut. Not surprisingly, the interplay between the dynamics of calcium and vitamin D often complicates the interpretation of data relative to calcium requirements, deficiency states, and excess intake.



Sources of calcium-

Calcium intake is usually associated with intake of dairy products such as yogurt, milk and cheese, as they are rich sources of calcium. Calcium rich sources are dairy products, especially per 100g, whereas milk and yogurt can provide between 100mg to 180mg per 100g. Cereals usually have around 30mg per 100g, however if they are fortified the amount can reach 180mg per 100g. Nuts and seeds are also rich in calcium, especially almond, sesame and chia that provide between 250 to 600 mg per 100g.

Vegetables rich in calcium are kale, broccoli and watercress, which provide between 100 and 150 mg per 100g. However, the impact of these food have on the total calcium intake depends on the population food consumption patterns.

- Some Asian countries have higher proportion of total calcium intake from non-animal foods such as vegetables, legumes and grains than from dairy products, though they also have much lower calcium intake.

Supplements are also a great dietary source of calcium for some populations. Some calcium supplements, available with no prescription, have up to 1000mg of calcium per tablet, which represent the nutritional requirements for most adults. However, the use of supplements also varies between countries. In United States and Canada, around 40% of the adult population was reported to have taken calcium supplements in the month before the interview and this figure increased to 70% in the older women group. On the other hand, in Argentina and in Holland very few women reported taking calcium supplements, even during pregnancy.

Calcium Recommendation-

Calcium requirements are high during all stages of life. Dietary reference values for individuals over 19 years of age vary from 1000 mg to 1300 mg depending on the reference guidelines.

The calcium requirement is different based on our gender and age.

The chart is given below.

Age Group	Mg/day
71+ Years (Elderly)	1200mg
19-70 Years (Men)	1000mg
51-70 Years (Women)	1200mg
19-50 Years (Women)	1000mg
9-18 Years (Boys+Girls)	1300mg
4-8 Years (Children)	1000mg
1-3 Years (Children)	700mg
0-6 Months (Infants)	200mg
Pregnant + Breastfeeding Women	1000-1300mg

Calcium Intake Effect On Blood Pressure-

Blood pressure is regulated by intracellular calcium in vascular smooth muscle cells, through vasoconstriction and variations of the vascular volume. Low calcium intake seems to trigger both mechanisms, raising plasma parathyroid hormone levels, that increase intracellular calcium directly or through calcitriol activation and stimulating the renin-angiotensin-aldosterone signalling pathway that produce sodium and water reabsorption, thus increasing the vascular volume.

Parathyroidectomized rats in comparison with shamoperated rats did not show an increase in blood pressure after 10 weeks of calcium-free diet. There is no established threshold for the benefits of calcium intake on blood pressure; in human and animals with low calcium intake, blood pressure is improved when calcium intake is increased to reach the recommended levels. No benefits for blood pressure by increased calcium intake have been observed in humans and animals with adequate calcium intake.

Calcium intake during pregnancy-

The effect of calcium supplementation during pregnancy has also been explored. The follow up of children whose mothers were involved in a RCT of calcium supplementation showed that children whose mother were in the calcium group had a reduction in the risk of high blood pressure at seven years of age in comparison with children whose mothers were in the placebo group. A systematic review shows that children whose mothers received calcium supplementation had a reduction of 1.92 mm Hg in SBP at age 1 to 9 years.

A follow up until 52 weeks of age of offspring of rats whose mothers had a low calcium intake during pregnancy showed values of SBP of 12.1 mm Hg.

Calcium intake on bone health-

A systematic review from 2006 that included 19 studies involving 2859 children found that the calcium supplementation had small effect on the total body bone mineral content and upper limb bone mineral density and this effect persisted after the end of supplementation only for the upper limb bone mineral density. The benefits of calcium supplementation seem to be greater in children and adolescents with low calcium intake.

Calcium effects in other age groups were usually evaluated in combination with vitamin D, so data for calcium alone are limited.

Disease caused due to calcium intake-

Hypercalcemia or high calcium levels may not cause any symptoms. However, serious hypercalcemia can cause excessive thirst, stomach pain, and confusion, among other symptoms.

High calcium levels in the blood (hypercalcemia) can result from an overactive parathyroid gland, too much vitamin D, some medications, and various underlying conditions, including cancer.

Calcium plays an essential role in the body. It helps build strong bones and teeth while also supporting the muscles, nerves, and heart. However, too much calcium can lead to problems.

What is hypercalcemia?

The parathyroid glands are responsible for controlling calcium levels in the blood. These four tiny glands sit behind the thyroid gland.

When the body needs calcium, the parathyroid glands secrete a hormone. This hormone signals:

- The bones to release calcium into the blood
- The kidneys to excrete less calcium into the urine
- The kidneys to activate vitamin D, which helps the digestive tract absorb more calcium

Overactive parathyroid glands or an underlying health condition can disrupt the balance of calcium.

If calcium levels become too high, a person may receive a diagnosis of hypercalcemia. This condition can impede bodily functions and may specifically lead to:

- poor bone health
- pancreatitis
- kidney stones
- abnormal heart and brain function
- Extremely high levels of calcium in the blood can become life threatening.

Symptoms

▪ Muscle problems-

A person with a calcium deficiency may experience:

- muscle aches, cramps, and spasms
- pain in the thighs and arms when walking or moving
- numbness and tingling in the hands, arms, feet, and legs, as well as around the mouth.
- Extreme fatigue-

Low levels of calcium can cause extreme fatigue, which involves a lack of energy and an overall feeling of sluggishness. It can also lead to insomnia.

Fatigue associated with a calcium deficiency can also involve lightheadedness, dizziness, and brain fog — characterized by a lack of focus, forgetfulness, and confusion.

▪ Nail and skin symptoms-

A lasting calcium deficiency can cause-

- dry skin
 - dry, broken, or brittle nails
 - coarse hair
 - alopecia, which causes hair to fall out in patches
- eczema, or skin inflammation that can lead to itchy or dry patches
- psoriasis.

▪ Osteopenia and osteoporosis-

The bones store calcium well, but they require high levels to stay strong. When overall levels of calcium are low, the body can divert some from the bones, making them brittle and prone to injury.

Over time, having too little calcium can cause osteopenia, a reduction of mineral density in the bones.

This can lead to osteoporosis, which causes the bones to thin and become vulnerable to fractures, as well as pain and problems with posture.

It can take takes years for osteoporosis and other complications of a calcium deficiency to develop.

▪ Dental problems-

When the body lacks calcium, it pulls it from sources such as the teeth. This can lead to dental problems, including:

- tooth decay
- brittle teeth
- irritated gums
- weak tooth roots

Also, a calcium deficiency in an infant can impair tooth development.

▪ Depression-

Some evidence Trusted Source suggests that calcium deficiency may be linked with mood disorders, including depression, though confirming this will require further research.

Anyone who suspects that a calcium deficiency is contributing to symptoms of depression should consult a doctor. After checking the person's calcium levels, the doctor may recommend a calcium supplement.

Treatment and prevention-

The safest and easiest way to treat or prevent a calcium deficiency is to add more calcium to the diet.

▪ Some calcium-rich foods include:

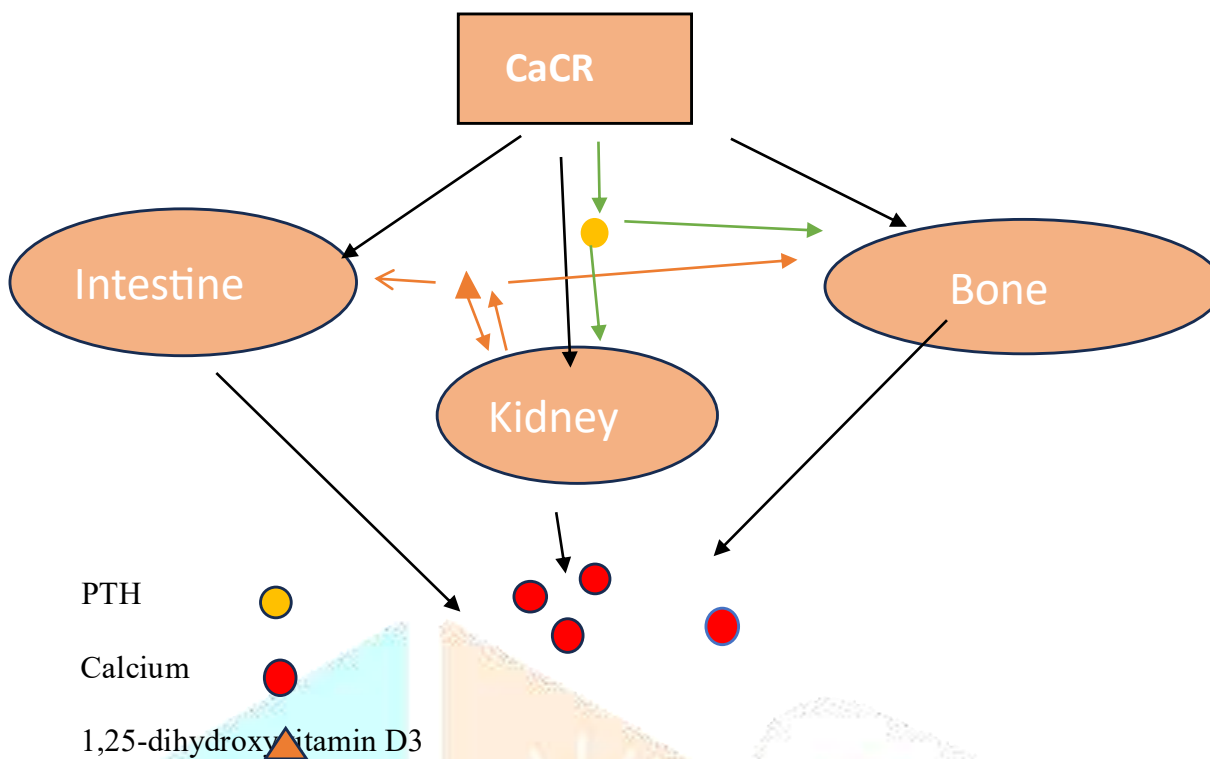
- dairy products, such as milk, cheese, and yogurt
- beans
- figs
- broccoli
- tofu
- soy milk
- spinach
- fortified cereals
- nuts and seeds, including almonds and sesame seeds.

Signaling Mechanism

The regulation by calcium sensing receptor (CaSR) located in the parathyroid gland, the concentration of extracellular calcium is dedicatedly maintained by intestinal absorption, kidney reabsorption and bone resorption/formation. The miscommunication of these processes is responsible for calcium-related diseases, such as osteomalacia . Americans at all ages, however, do not consume enough dietary calcium compared with the recommendations by the Institute of Medicine . The deficiency of calcium could cause various diseases, such as osteoporosis. In this paper, we will review the key factors controlling calcium homeostasis and further discuss the diseases associated with the dysfunctional regulation of calcium and vitamin D.

• Molecular mechanism of extracellular calcium homeostasis-

Extracellular calcium homeostasis is mainly controlled by three physiological modes, including intestinal calcium absorption, renal calcium reabsorption, and bone formation/resorption , which is mainly regulated by CaSR through the modulation of parathyroid hormone (PTH), calcitonin and 1,25-dihydroxyvitamin D₃ secretion.

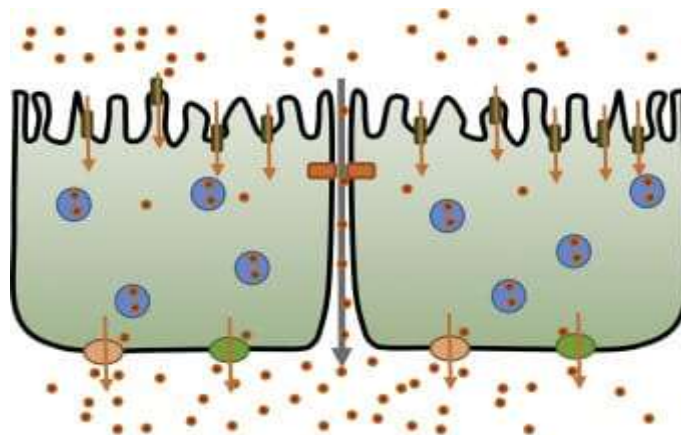


Regulation of calcium homeostasis by CaSR. The decrease of blood calcium level activates CaSR in parathyroid gland, which further promotes the secretion of PTH. PHT increases blood calcium level by the direct activation of calcium reabsorption in kidney and calcium release in bone. PHT also promotes the production and secretion of 1,25-dihydroxyvitamin D3 in kidney cells. 1,25-Dihydroxyvitamin D3 regulates the intestinal calcium absorption, kidney calcium reabsorption and bone calcium release. CaSR expressed in bone, kidney and intestine cells are also involved in the regulation of calcium homeostasis.

Calcium uptake in intestine -

Intestine is the major organ responsible for calcium uptake. In general, calcium from diets is absorbed by intestine through two pathways including transcellular absorption and paracellular transport of calcium. In duodenum of intestine, transcellular absorption is responsible for 80% calcium uptake in low-calcium diets and less than 10% calcium uptake in high-calcium diets. Certain calcium channels, intracellular calcium-binding proteins and calcium pumps are responsible for transcellular absorption of calcium. This process is initiated by transient receptor potential vanilloid type 6 (TRPV6) channel, a transmembrane calcium selective channel located in the brush border side membrane responsible for calcium entry. After calcium enters the cell through TRPV6 channel, calcium-buffering proteins bind to calcium and transport calcium inside the cell. At last,

calcium is excluded out of the cell to blood vessels through plasma membrane ATPase 1b (PMCA1b) located in the basolateral membrane.

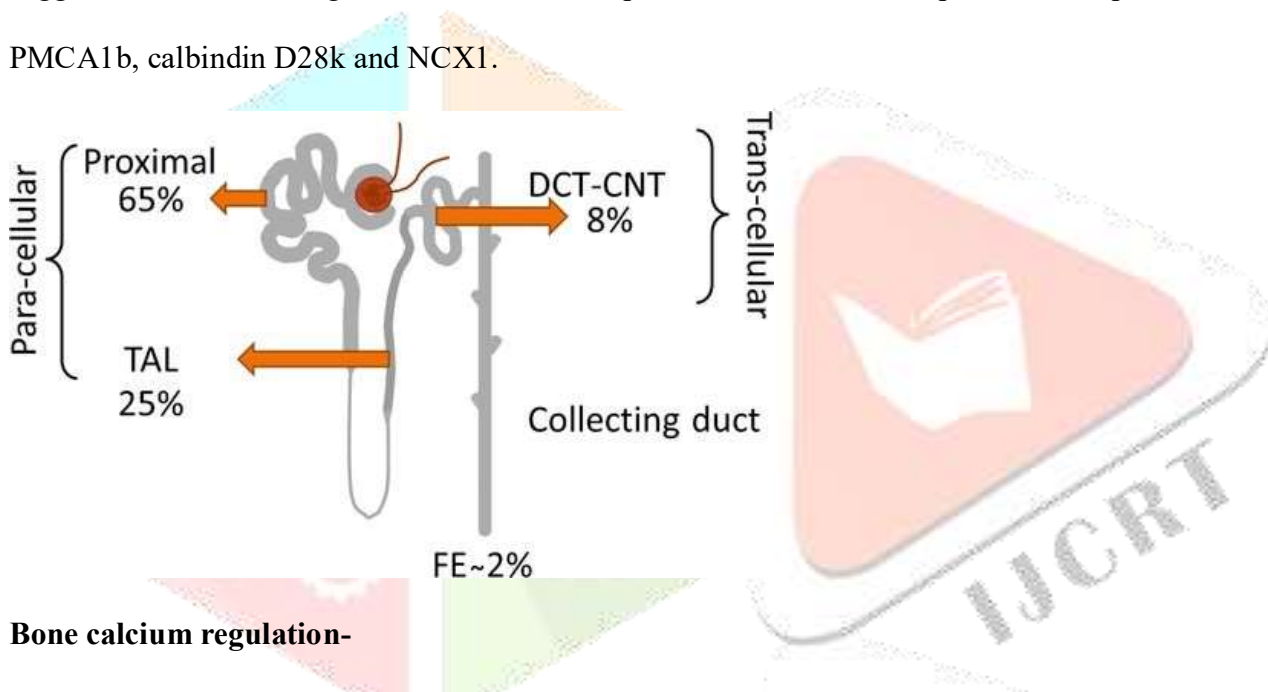


Calcium reabsorption in kidney-

Kidney is another essential organ for calcium sensing and reabsorption. Calcium is absorbed in nephron with the highest absorption in proximal tubules. The renal calcium reabsorption comprises of two pathways including paracellular pathway and transepithelial pathway. Similar as transcellular calcium absorption in intestine, transepithelial calcium reabsorption in kidney also contains three major steps. First, calcium is transported to the intracellular space through calcium channels located in the apical membrane. TRPV5 is the major calcium channel located in the apical plasma membrane responsible for calcium transportation. TRPV5 is a calcium-selective channel with 75% amino acid identity to TRPV6. The N-terminal of TRPV5 contains six ankyrin repeats involved in the tetramer formation and protein-protein interaction. The C-terminal of TRPV5 contains a phosphorylation site of protein kinase C. The kidney calcium reabsorption is impaired in TRPV5 knockout mice, suggesting the critical role of TRPV5 in this process. TRPV5 is regulated by many biomolecules, and can be activated by kallikrein or bradykinin receptor through PLC/DAG/PKC pathway. Similar to TRPV6, TRPV5 is regulated by annexin-2, Rab11a, calmodulin and other proteins. Second, the intracellular calcium binds to calcium-buffering proteins, such as calbindin D28k and calbindin D9k, and passively diffused to the basolateral membrane through calcium gradient. Calbindin D28k contains three pairs of EF-hand motifs with 6 calcium-binding sites. This protein dynamically controls calcium reabsorption through the interaction with TRPV5 at low intracellular calcium concentration. Renal calcium reabsorption is disrupted in calbindin D28k knockout mice with high calcium diets, while other group shows that the effect of calbindin

D28k on calcium transport is compensated by other proteins including calbindin D9k. At last, calcium is transported to blood by PMCA1b and/or NCX1 located in the basolateral membrane.

Calcium reabsorption in kidney is modulated by PTH, 1,25-dihydroxyvitamin D3 and estrogen. PTH reduces the expression levels of TRPV5, calbindin D28k, PMCA1b and NCX1 in kidney cells through PTH receptor (PTHrP)-mediated signaling pathway. PTH also stimulates the production of 1,25-dihydroxyvitamin D3 in proximal tubules. 1,25-Dihydroxyvitamin D3, produced from kidney and other organs, down-regulates the expression of TRPV5, NCX1 and calbindin D28k in kidney cells. The expression level of PMCA1b in these cells, however, is not significantly affected by 1,25-dihydroxyvitamin D3. Additionally, animal experiments also suggest that certain estrogen can increase the expression of renal reabsorption-related proteins, such as TRPV5, PMCA1b, calbindin D28k and NCX1.



Bone calcium regulation-

Besides intestinal absorption and renal reabsorption of calcium, bone resorption is an important mechanism to modulate calcium level in blood. Bone is constantly remodeled by osteoblasts and osteoclast. Osteoblasts facilitate bone formation, while osteoclasts break bone tissue and release calcium. The development and activation of osteoclasts are mediated by receptor activator of NF- κ B (RANK) ligand (RANKL). The expression of RANKL is promoted by vitamin D3, PTH, PTHrP, TNF- α , IL-1, IL-6, IL-11 and IL-17 and inhibited by TGF- β . On the other hand, the activity of RANKL is also inhibited by osteoprotegerin (OPG), a secreted protein functioning as a decoy receptor for RANKL. OPG disrupts the interaction between RANK and RANKL by competitively binding to RANKL, and functions as an inhibitor for the development and activation of osteoclasts. The expression level of OPG in human bone marrow cells is inhibited by 1,25-dihydroxyvitamin D3 and PTH.

Thus, 1,25-dihydroxyvitamin D₃ and PTH modulate calcium resorption in bone by increasing RANKL expression and decreasing OPG expression.

Calcium diets, supplements, vitamin D and diseases-

Food is an important source for calcium uptake. The common calcium-rich foods include milk, yogurt, cheese, shrimp, soybean, soy milk, tofu, broccoli, orange, kale and others. The major forms of calcium supplements are calcium carbonate and calcium citrate. Americans at all ages, however, do not take enough dietary calcium compared with the recommendations by the Institute of Medicine. Sufficient calcium intake is important for human health and calcium deficiency could lead to diseases, such as osteoporosis and rickets.

Bone is a living and constantly remodeling tissue. The old or damaged bone is resorbed by osteoclasts and the new bone is constructed by osteoblasts. Bone is primarily composed of organic components and inorganic components. The organic components are consisted mainly of type I collagen responsible for bone flexibility. The inorganic components comprised of hydroxyapatite, insoluble salts containing calcium and phosphorus provide bone strength against compression. The concentration of calcium in serum is usually kept in a very limited range so as to prevent the disorder of some physiological functions, such as muscle contraction. Bone is a mineral reservoir for calcium and phosphorus. Over 99% of total calcium in human body is stored in bone and teeth. Calcium plays important roles in the formation process of new bone and maintenance of existing bone by collaborating with other factors such as phosphorus, vitamin D and calcium-binding proteins.

Dietary calcium intake is critical for the calcium homeostasis of bone. Supplementary diets containing calcium with average recommended dietary allowance for children increase bone mineral density (BMD) and reduce the risk of fracture. As reviewed in the previous section, calcium homeostasis is well maintained in the cells from intestine, kidney and bone. When serum calcium level is low, CaSR promotes the secretion of PTH and indirectly increases 1,25-dihydroxyvitamin D₃ level. When dietary calcium intake from intestine is low, blood calcium level is maintained by kidney reabsorption and bone calcium release at the expense of bone strength. On the other hand, lack of vitamin D could cause serious health problems. Low vitamin D level limits the synthesis of

1,25-dihydroxyvitamin D₃, which further reduces blood calcium level through the inhibition of intestinal calcium absorption and renal calcium absorption. The PTH level, however, increases in response to the reduced blood calcium level. The increase of PTH promotes bone remodeling, while low calcium inhibits bone mineralization, correspondingly leading to the increased osteoid.

Some studies have demonstrated that patients with specific diseases or disease treatments may have skeletal abnormalities. For example, valproate, a chronic antiepileptic therapy, may cause low bone mass in pediatric patients and sufficient intake of calcium can offset this harmful effect. BMD is significantly lower in patients with Parkinson's disease than the healthy people and the lower BMD is correlated with severe progression of the disease. The loss of BMD is the early sign of osteopenia that can turn into osteoporosis. Osteoporosis can lead to fracture and other severe bone diseases. Current studies reveal that adequate intake of calcium can decrease the risk of osteoporosis, fracture and diabetes in some cases.

The role of calcium in cancer has been explored for almost 100 years. The relationship between calcium and cancer, however, is still controversial. A previous randomized trial has demonstrated that the supplementation of calcium and vitamin D for seven years has no effects on colorectal cancer. High calcium intake, however, seems to reduce the risk of breast cancer and the increase the risk of prostate cancer. Breast cancer is the most common cancer in women in the United States and China. Early diagnosis, prognosis and treatment of cancers through biomarkers, such as HER-2 and gastrin-releasing peptide receptor (GRPR), are actively studied in animal models. On the other hand, cancer prevention through diet interventions is a hot topic with the aim of reducing and preventing cancer occurrence. High calcium intake seems to reduce the risk of some cancers, such as breast cancer. Vitamin D and calcium shows anti-breast cancer effects through regulating signaling pathways associated with cell proliferation, invasion and apoptosis. Epidemiological studies show that the intake of dietary and supplementary calcium and vitamin D reduces the risk of breast cancer. Additionally, the levels of serum calcium and vitamin D metabolites are inversely correlated with breast cancer. The mutations in vitamin D receptor and calcium sensing receptor are also identified in breast cancer tissue, suggesting the involvement of calcium and vitamin D signaling in breast cancer. TRPV6 can exhibit the up-regulation by 2–15 folds in breast cancer tissue when compared with that in normal breast tissue. The expression level of TRPV6 is reduced in breast cancer cell lines in the presence of tamoxifen, an antagonist of estrogen receptor, and can be up-regulated by 1,25-vitamin

D. The overexpression of TRPV6 is also observed in the highly invasive area of breast cancer. Therefore, further studies on the relationship between dietary vitamin D/calcium and TRPV6 in breast cancer are highly desired. Additionally, dietary calcium involves in cardiovascular diseases. High calcium intake could induce fatty acids and bile to bind to calcium, which further inhibits intestinal calcium absorption and therefore reduces cholesterol level in blood. Blood calcium also regulates blood pressure by modulating renin-angiotensin system.

Whether calcium supplements can be beneficial or harmful to the health of people is still controversial. Although the effects of calcium supplements or casual calcium uptake on health outcomes have been systematically reviewed, the risks of calcium supplements for cardiovascular diseases have not been completely understood. High calcium intake can slightly improve BMD in children and pregnant woman. There is no consistent conclusion between calcium intake and cardiovascular diseases, except blood pressure. Similarly, although some studies show that people with high calcium intake has lower chance of overweight and obesity, the relationship between calcium and obesity is still controversial. Calcium supplementation in diets can contribute to the reduced rate of bone loss and fracture incidence in elders; however, it can also increase the risks of acute gastrointestinal events, kidney stone, and cardiovascular diseases such as myocardial infarction and stroke. Based on the meta-analysis, only 10% fracture incidence is reduced due to the calcium supplementation, but the incidences of myocardial infarction and stroke are increased up to 27%–31% and 12%–20%, respectively. Moreover, high calcium intake for men also has the potential for the risk of advanced and fatal prostate cancer.