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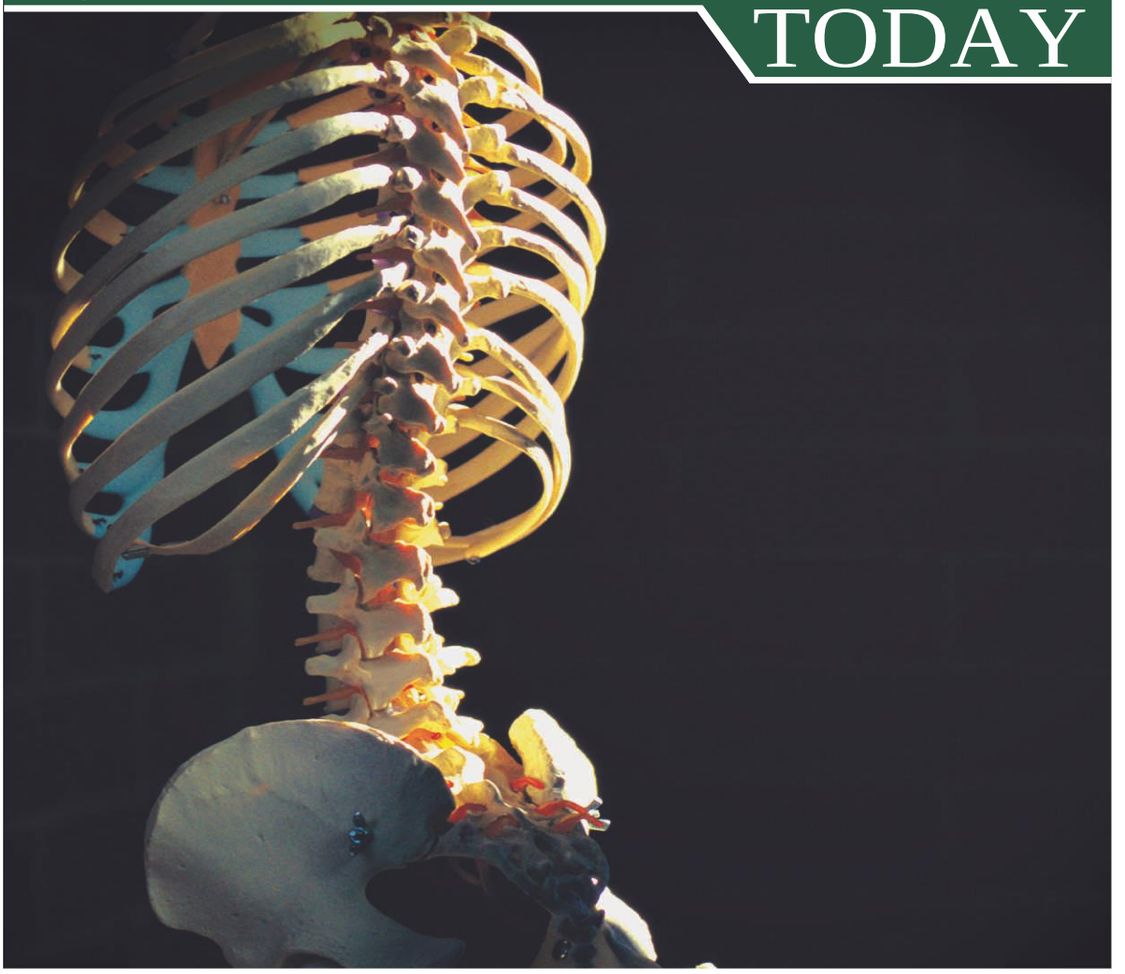

MINERAL TRANSPORTERS – THE NOVEL APPROACH IN MANAGEMENT OF BONE HEALTH AND OSTEOPOROSIS

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OSTEOPOROSIS

Mineral Transporters – The Novel Approach in Management of Bone Health and Osteoporosis

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ABSTRACT
Osteoporosis is a condition characterized by a decrease in the density of bone. Mineral transporters are electrically neutral compounds formed by joining of carrier molecules (like aspartic acid and orotic acid) with minerals (like calcium) that have different transport properties than unbound ionized minerals. Calcium orotate and calcium aspartate are some of the mineral transporters which are acid resistant and used for the treatment of osteoporosis.

"The number of hip fractures worldwide is expected to increase from 1.3 million in 1990 to 6.3 million in 2050, with most of the future hip fractures occurring in Asia"

OSTEOPOROSIS

Osteoporosis is a condition characterized by a decrease in the density of bone, decreasing its strength and resulting in fragile bones. Osteoporosis is a clinically silent but progressive disease until a fracture occurs. In UK the disorder results in over 200,000 fractures a year, at an annual cost of over £940 million a year to the National Health Service. The epidemiology of fractures is very different in different parts of the world. In Europe, the number of people over 65 is expected to reach a figure of 133 million from only 68 million in 1990, whereas in Asia the number is likely to grow from 145 million to 894 million during the same period. The demographic trend alone could increase the number of hip fractures worldwide to increase from 1.3 million in 1990 to 6.3 million in 2050, with most of the future hip fractures occurring in Asia.[1] The expected increase in hip fractures in World wide terms by 2050 is 8.2 million assuming the annual rise in the range of 1% for age adjusted incidence. Even if rates of fractures stabilized in Europe and North America but rose by 3% per year in the rest of the world, the total could well exceed 21 million.[2] The only data from Asian continent has been from China where there is a rapid rise of hip fractures, which is predominantly attributed to decline in physical activities and urbanization effect besides the usual factor common to all parts of the world such as increase in the length of life in general. Commonest sites of fractures are the Hip and the Spine and most studies refer to these fractures extensively.

Keywords : *Osteoporosis, mineral transporters, calcium aspartate, calcium orotate*

OSTEOPOROSIS- CURRENT SCENARIO IN INDIA

The incidence, in general, is higher among women and older people. The reason it is lower among men is that their bones are bigger and hence less likely to break. And also, men tend to live not as long as women. But now as men also tend to live longer, the incidence among them is also increasing.

With increasing longevity of the Indian population, it is now being realized that, as in the West, osteoporotic fractures are a major cause of morbidity and mortality in the elderly. There are two interesting points about the disease in India - the

high incidence among men and the lower age of peak incidence compared to Western countries. Data suggest that the incidence of hip fracture - which is easily picked up by epidemiology studies as those with hip fractures end up in hospitals - is one woman to one man in India, while in places like Australia it is three women to one man. In most Western countries, while the peak incidence of osteoporosis occurs at about 70-80 years of age, in India it may afflict those 10-20 years younger, at age 50-60. Based on 2001 census, approximately 163 million Indians are above the age of 50; this number is expected to increase to 230 million by 2015.[3] Even conservative estimates suggest that of these, 20 per cent of women and about 10-15 per cent of men would be osteoporotic. The total affected population would, therefore, be around 25 million. If the lower bone density is shown to confer a greater risk of fracture, as is expected, the figure can increase to 50 million.[4]

"Adequate calcium intake is the cornerstone of any osteoporosis prevention (or treatment) plan"

CALCIUM THERAPY FOR OSTEOPOROSIS

Adequate calcium intake is the cornerstone of any osteoporosis prevention (or treatment) plan. Calcium supplementation should occur whenever the recommended daily intake of calcium is not being met. It has been shown that calcium absorption decreases with advancing age, and that renal excretion of calcium increases. Intra- and extracellular levels of calcium are tightly controlled. Since bone is a major reservoir for calcium, bone mass may be sacrificed to maintain target intra- and extracellular concentrations. [5]

"Low vitamin D levels are associated with impairment of the active absorption of calcium. Low levels may be due to lack of dietary or supplemental vitamin D intake or lack of sun exposure"

As many modern diets do not provide the recommended levels of calcium, dietary calcium supplements have been recommended for prevention of osteoporosis. Many forms of dietary calcium supplements are widely available, but products containing calcium carbonate and calcium citrate are the most common.

LIMITATIONS OF CALCIUM THERAPY

Roughly 30% of calcium in foods is absorbed by adults, and the amount absorbed is dependent upon diet and levels that are available in the body.[6] The calcium supplements available are not able to provide the desired amount of calcium as the absorption of calcium is regulated by certain factors. It has to be soluble in the luminal fluid of the small intestine; second, it has to present itself in a singular molecule as an ionic entity, so that it will be able to penetrate the mucous membrane and be absorbed.

"Polymorphisms in vitamin D receptors (VDR) have been associated with variation in calcium absorption"

Poor bioavailability

There are number of factors which affect calcium absorption in the gut.[7] Absorption which is greatest when the intake of calcium is low and the need is high. Vitamin D levels, an acidic environment in the gut, age, estrogen levels, and dietary fibre intake all play a role in calcium absorption. Calcium absorption decreases with age, low vitamin D levels, hypochlorhydria, low estrogen levels, and a high-fiber diet.

The bioavailability of calcium supplements depends upon their solubility and absorption. For example, much of the calcium in supplements fails to be absorbed and passes out in the faeces, and much of the rest that does get absorbed into the blood then travels to the kidneys where it is excreted in the urine. In fact, calcium carbonate was found to be insoluble in water. The level of calcium circulating in the blood is tightly controlled by the parathyroid hormone, calcitonin, and calciferol (Vitamin D). All together, they regulate how much is absorbed from food and how much spills over into the urine. Low vitamin D levels are associated with impairment of the active absorption of calcium. Low levels may be due to lack of dietary or supplemental vitamin D intake or lack of sun exposure. In individuals with gross vitamin D deficiency, only 10%–15% of dietary calcium is absorbed. Calcium absorption varies, depending on serum 25-hydroxyvitamin D [25(OH)D] levels. In a study, absorption rates of calcium were 65% higher at serum 25(OH)D levels of 86.5 nmol/L than at levels averaging <50 nmol/L.[8]

In addition to dietary factors, genetics plays a role in bone density. Polymorphisms in vitamin D receptors (VDR) have been associated with variation in calcium absorption, although no consensus has been reached regarding their role in BMD.[9]

Individuals vary in their ability to absorb calcium. Calcium absorption averaged 35% and ranged from 17% to 58% in a study of 142 healthy pre- and peri menopausal women.[10] In this study, calcium absorption was inversely related to total dietary calcium intake, dietary fibre, alcohol intake, and physical activity. Calcium absorption was also positively associated with body mass index, dietary fat intake, and serum $1,25(OH)_2$ D and PTH levels. Women who had the lowest ratio of fat to fiber intake had a 19% lower absorption of calcium when compared with women with the highest ratio of fat to fibre intake. Polymorphisms in VDR were not associated with differences in calcium absorption in this study.

"Clinical study has shown poor bioavailability of calcium from calcium supplements. The total bioavailability of calcium absorption from different calcium preparation varies between 10% to 30%"

Clinical study has shown poor bioavailability of calcium from calcium supplements. The total bioavailability of calcium absorption from different calcium preparation varies between 10% to 30%. In a comparison study, it was revealed that calcium citrate has more bioavailability than calcium carbonate.

Calcium absorption from calcium citrate malate and calcium carbonate as tablets was measured in a two-period crossover study with 12 healthy adolescents (6 boys, 6 girls) ages 10-17 years, given 114.6 mg of elemental calcium enriched with 10.4 mg 44Ca as both salts (Miller *et al.*, 1988). Thirty minutes after ingestion, subjects received 3.6 mg 42Ca intravenously. Calcium absorption was calculated from the ratio of the tracer isotopes in 24-hr urine samples compared to the dose before tracer administration. There have been conflicting evidences suggesting the absorption of calcium from calcium carbonate and calcium citrate. However the recent available data states that the percentage absorption of calcium from calcium carbonate is 8.24% whereas calcium citrate is 27.12% absorption.[11]

"Due to the limitations of the calcium supplements, mineral transporters have evolved as a better treatment option for osteoporosis"

Gastrointestinal side effects

Calcium supplements are generally well tolerated, however, some patients complain of gastrointestinal symptoms, including constipation, gas, flatulence, and bloating. Although calcium carbonate is the form most often associated with these reported side effects. In addition, it is important to determine if lack of fluid or fiber is the cause of constipation. Other causes of gas and bloating, such as lactose or fructose intolerance, food sensitivities, dysbiosis, or celiac disease, should be investigated if symptoms do not improve after changing to calcium citrate.[12]

Table 1: Food interactions with calcium

Food	Interaction with Conventional Calcium
Fibre	Phytic acid can decrease calcium absorption. Psyllium does not seem to significantly decrease calcium absorption.
Iron, zinc, magnesium	Calcium supplements may decrease the absorption of iron, zinc, and magnesium.
Caffeine	Caffeine intake 300 mg/d increases urinary excretion of calcium.
Sodium	Sodium increases urinary calcium excretion.

Drug and food interactions

There are multiple drug-nutrient interactions associated with calcium supplements. Calcium supplements are widely used, and the risk for interactions is therefore elevated. Patients should be asked about calcium supplement use and educated on potential drug-nutrient interactions. Table 1 summarize some of the food interactions

EMERGENCE OF MINERAL TRANSPORTERS

Due to the limitations of the calcium supplements, mineral transporters have evolved as a better treatment option for osteoporosis. In osteoporosis biological utilization of minerals includes mineral absorption, mineral transport in the blood stream and mineral delivery into the target tissue. Most mineral supplements generally break apart during the processes of digestion releasing ionized minerals into the lumen of the digestive tract, which are then moved into the bloodstream. Just getting a mineral into the blood stream does not guarantee that the mineral can be directed to any particular tissue or be transported across the cell membrane to the cell interior.[13,14]

What are mineral transporters?

Mineral transporters are electrically neutral compounds formed by joining of carrier molecules (like aspartic acid and orotic acid) with minerals (like calcium) that have different transport properties than unbound ionized minerals.[15] Calcium orotate and calcium aspartate are some of the mineral transporters which are acid resistant.

Advantages of Mineral Transporters

- Better bioavailability
- Stability
- No food interaction
- Do not cause kidney stones and GI side effects
- Wide pH solubility (4-11)
- Site specific action

Properties of mineral transporters

They deliver minerals still bound to the transporter into the alkaline environment of the small intestine where the mineral compounds are absorbed relatively intact from the digestive tract into the blood stream with the mineral still bound to the transporter.[15]

Mineral transporter complex

The mineral-transporter complex remains stable in the blood stream with low dissociation, and the minerals are not released until the mineral-trans-

"Calcium orotate and calcium aspartate are efficient mineral transporters for conditions associated with calcium loss in bone tissue and are excellent vehicles for delivering bioavailable minerals (calcium) to bone tissue undergoing decalcification"

porter complex enters the target tissues/cells. The attachment of minerals to carrier molecules forms electrically neutral stable complexes that allow selective direction of minerals to particular tissues that metabolically use the carrier molecules. This form of directed mineral nutrition even enhances mineral entry even into cells that have disturbed cell membranes.

BIOLOGICAL ROLE OF MINERAL TRANSPORTERS IN BONE HEALTH

Calcium orotate and calcium aspartate are efficient mineral transporters for conditions associated with calcium loss in bone tissue and are excellent vehicles for delivering bioavailable minerals (calcium) to bone tissue undergoing decalcification. Because these mineral transporters can penetrate through cell membranes they can compensate for impaired calcium transport through cell membranes and be effective delivery compounds for intracellular supplementation of this mineral.

Calcium Orotate and Calcium Aspartate prove to be useful repair compounds in traumatic and inflammatory conditions where bone cells are damaged. These calcium mineral transporters have an affinity for the connective tissue of bone and intervertebral discs making them particularly beneficial in improving bone density and bone remodeling processes.[16,17]

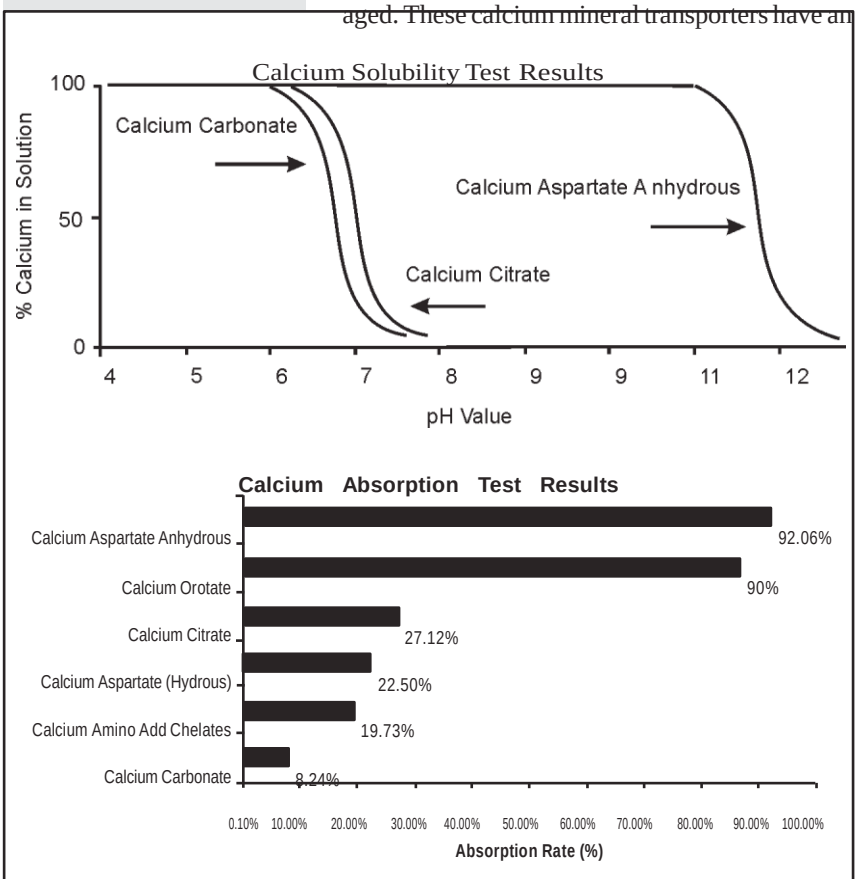

Fig. 1: Solubility and absorption rates of different calcium preparation

CALCIUM ASPARTATE ANHYDROUS (CAA) - THE MINERAL TRANSPORTER[18]

CAA is completely soluble in a wide range of pH (4.0-11.0). It is an organic compound formed of calcium atom and L-aspartic acid molecules. The calcium atom is strongly bound to ligands of L-aspartic acids to form unbreakable ties. L-aspartic acid fends off malicious attacks from inorganic compounds and transport calcium atoms to the small intestine, where absorption takes place. Hence food does not interfere with absorption of CAA.

Calcium Aspartate is made from natural soluble calcium and chelated with the amino acid, L-Aspartate. Calcium Aspartate extends the calcium absorption from the duodenum to the entire length of the small intestine and therefore achieves the absorption rate much superior to those of other calcium products (Fig. 1). Its unprecedented calcium absorption rate which is as high as 92.06% is up to 20 times higher than that of any other calcium supplement[19]

CAA is obtained from plant source, hence is organic in nature.

Due to wide pH solubility, CAA does not precipitate in alkaline environment of small intestine; hence does not cause gelatinous magma precipitation.

CAA is well tolerated and does not cause diarrhoea, constipation or malabsorption of nutrients.

Being a mineral transporter, CAA is absorbed in the molecular form in the blood. Due to this fact, CAA does not possess any risk of kidney stones to the patients with the history of renal calculi.

CALCIUM OROTATE-THE MINERAL TRANSPORTER

Calcium Orotate is a mineral transporter in which orotic acid forms a high complex salt with calcium which has no metabolic affinity to outer cell membrane of osteoblast, rather it penetrates the outer cell membrane in intact form and assimilates calcium inside the bone matrix. It is most active in providing treatment for bone decalcification. It has a pronounced anti-inflammatory effect in orthopedic conditions such as arthritis. In fact, it can be very effective in re-calcifying the bone tissue

"Calcium Orotate penetrates the outer cell membrane of osteoblast and delivers calcium ion inside the cell near mitochondria"

following extensive radiation treatment of cancerous bone lesions. Calcium Orotate really performs clinical effects in various diseases connected with decalcification and injury of bones.[20]

The pentose pathway is involved in the metabolic processes of cartilage, blood vessels, connective tissue, bone matrix and ligaments. Because orotic acid is a substrate in the pentose phosphate pathway, orotate mineral transporters are able to bioaccumulate in tissues such as bone that use this pathway. This is how Calcium Orotate penetrates the outer cell membrane of osteoblast and delivers calcium ion inside the cell near mitochondria.[21,22]

ROLE OF CALCIUM ASPARTATE ANHYDROUS IN BONE HEALTH[23]

Calcium Aspartate after absorption reaches to the inner layer of the outer cell membrane of Osteoblast and there, upon metabolization releases the calcium to become the ion.

Increases bone density by stimulating Osteoblast (bone forming cells) activities to make sure calcium is converted to bone mass.

Promotes collagen production.

Adds tenacity and flexibility to the bones.

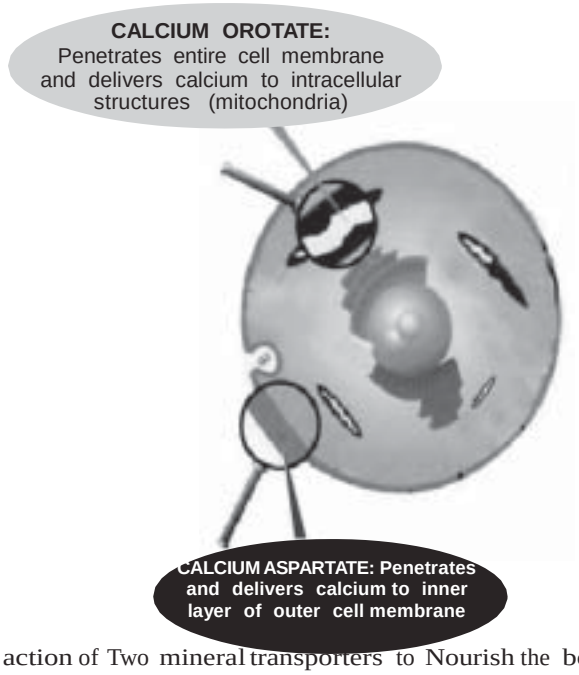

Fig. 2: Dual action of Two mineral transporters to Nourish the bone

Table 2: Comparison of the effect of calcium aspartate and citrate on BMD

Preparation	After 3 Months BMD		After 12 Months BMD	
	Lumbar Spine	Total Hip	Lumbar Spine	Total Hip
Calcium Aspartate	□4.07%	□3.37%	□5.66%	□4.11%
Calcium Citrate	□0.64%	No Change	□0.51%	No Change
Placebo	No Change	No Change	□0.75%	□1.17%

A study was conducted to evaluate the efficacy of calcium aspartate in which 1306 osteoporotic patients were assigned to receive calcium aspartate anhydrous and a placebo, or calcium citrate and vitamin D, or two placebos.

After 3 months, results showed that the bone mineral density (BMD) at the lumbar spine had increased by a mean of 4.07% in calcium aspartate anhydrous group, 0.64% in the calcium citrate group and there was no significant change in the double placebo group. The BMD of the total hip had increased by a mean of 3.37% in the calcium aspartate anhydrous group and no significant changes were seen in calcium citrate group. At 12 months, lumbar spine BMD had increased by a mean of 5.66% in the calcium aspartate anhydrous group, while the calcium citrate group and the double placebo group showed decline of 0.51% and 0.75% respectively. Total hip BMD increased by a mean of 4.11% in the calcium aspartate anhydrous group while there was no significant change in the calcium citrate group. Total hip BMD declined by a mean of 1.17% in the double-placebo group (Table 2). It was concluded that calcium aspartate anhydrous increases bone mineral density significantly. Calcium citrate plus vitamin D may help slow bone loss at the hip.

Role of Calcium Orotate in bone health[24]

Calcium orotate penetrates the outer cell membrane of osteoblast and releases calcium ion only at the sites of membranes of the mitochondria and the structures found in cell plasma (Fig. 2).

Effectively treats both inflammatory and osteoporotic decalcification.

Prevents degenerative bone changes in Osteoarthritis

Orotic acid forms a high complex salt with any mineral and has no metabolic affinity to the outer cell membrane but penetrates the outer cell membrane even in the form of a complex salt and is only metabolized at the site of the membranes of the mitochondria and of the structures found in the cell plasma. Binding of orotic acid with min-

eral results in a stable electrically neutral salt. Calcium orotate really performs clinical effects in various diseases connected with decalcification and injury of bones which can rapidly be improved by means of the application of calcium orotate by using this new concept of active mineral transport. Calcium orotate is useful in treating both inflammatory and osteoporotic decalcification and in relieving pain resulting from osteoporosis of the spine. In another study, successful recalcification of malignant bone tumors (thereby preventing further metastases) with calcium orotate in 10 out of 13 subjects[1] has been reported. A further paper study reported on the benefits of calcium orotate in treating joint diseases such as arthritis and spondylitis. On the basis of results such as these, it seems likely that calcium orotate can also have a beneficial impact on the degenerative bone changes characteristic of osteoarthritis.

"Calcium orotate is useful in treating both inflammatory and osteoporotic decalcification and in relieving pain resulting from osteoporosis of the spine"

CONCLUSION

Calcium is essential for the strengthening of bones, muscle and nerve function. Although most people are aware of this, calcium is severely deficient in most of our diets. As a result, we are experiencing an epidemic of osteoporosis in our life. The human body is constantly building and destroying bone mass. As long as it is receiving sufficient calcium, exercise, and hormones, bone building stays ahead of bone loss; osteoporosis occurs in older people when bone loss outpaces their bone building. For the treatment of osteoporosis there are many calcium supplements available, most common is calcium carbonate; others include calcium citrate-malate, calcium lactate, and calcium gluconate. But these calcium supplements are having limitations of poor bioavailability, food interactions and other side effects. These limitations are over come by mineral transporters such as calcium aspartate and calcium orotate which are having high bioavailability, site specificity, good tolerability, no risk of kidney stones and no food interactions and therefore better patient compliance. Thus, these mineral transporters are proving to be better alternatives for the treatment of osteoporosis.

"Calcium aspartate and calcium orotate have high bioavailability, site specificity, good tolerability, no risk of kidney stones and no food interactions and therefore better compliance"

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