



## Reviewing the Analeptic Activity of Calcium Citrate Malate

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### ABSTRACT

Calcium Citrate Malate's (CCM) health benefits were patented over three decades ago. It is involved in calcium retention, in children and adolescents. In adulthood, it is seen to promote the maintenance of bone health. In conjunction with vitamin D, CCM also decreases the risk of bone fracture in aged people and ensures that postmenopausal women's health is made better. CCM, unlike other supplements, does not need to be taken along with a meal and is seen to deliver benefits to individuals of any age group. CCM is usually used when the person has achlorhydria where the gastric acid secretion is reduced and there is an absence of an acidic environment (required by calcium carbonate). Calcium citrate Malate possesses outstanding bioavailability properties and is a useful extension to the calcium available presently, either for direct supplementation or for food fortification.

**Keywords:** Calcium Citrate Malate, Dental care, Gynaecology, Calcium deficiency, Osteoporosis.

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### INTRODUCTION

The most abundant mineral in the human body is calcium. Calcium deficiency can lead to osteoporosis. It can be prevented by various calcium preparations, organic salts like tricalcium citrate, calcium lactate, calcium lactate gluconate, calcium gluconate, and inorganic salts like calcium chloride, calcium carbonate, and calcium phosphate.<sup>1</sup>

Public awareness of the importance of adequate calcium in the diet has led to a greater demand for supplements and calcium supplementation. Calcium solubility is believed to be an important factor in its absorption.<sup>2</sup> The main function of consuming calcium is to strengthen the skeleton. Insufficient consumption of calcium during the early stages of life hinders the development of bone and further fractures in adulthood.<sup>3</sup> Calcium is present in blood, muscle, and cell fluids. It is present both in plant and animal foods. Amongst the animals' food, the major source is milk and its products and amongst the plants, it is green leafy vegetables. There are 6 calcium salts<sup>4</sup>-

- 1) lactate
- 2) carbonate
- 3) citrate
- 4) gluconate

- 5) phosphate
- 6) citrate malate.

Rapidly increasing awareness of bone health has increased the demand for different types of Ca supplements and Ca fortified food products.<sup>5</sup> Calcium carbonate and calcium citrate are the most common calcium supplements that are taken by a large variety of people. This is because calcium carbonate is affordable.<sup>5</sup> Calcium supplements are consumed by people more than 50 years of age. Studies suggest that high calcium intake may prevent vascular diseases. However, calcium supplements increase vascular calcification and increase the mortality rate in patients with renal failure.<sup>3</sup> CCM is a metastable compound consisting of calcium salts of citric acid and malic acid. The structure of CCM is unknown. It is present as a mixture of various crystalline and non-crystalline forms.<sup>5,8</sup> It exists in several stages of hydration. It has a molecular ratio of 6:2:3 of calcium: citrate: malate.<sup>2,5</sup> The structure of CCM makes it possible and easily soluble in the stomach than calcium citrate. Calcium citrate malate is well-absorbed taken with or without food. CCM is a composite salt with 10 times more solubility than Calcium citrate or calcium malate independently. Ca absorption from CCM fortified orange/apple juice is more than from milk and Calcium carbonate.<sup>7</sup> The chemistry of CCM makes it a particularly beneficial calcium source for individuals with hypochlorhydria or achlorhydria, which generally includes the elderly and those on medications that decrease gastric acid secretion.<sup>1</sup> Calcium Supplementation is available commercially in different forms. These forms are said to have different levels of efficacy amongst different people. This efficacy can also differ through the method that it is administered and based on the individual. Calcium is essential for the metabolic functioning of the body. There is a certain level



of Calcium required by the body to function properly. When that level drops below the threshold, there are bone defects and can lead to metabolic disorders in the long run.

The calcium balance in the body is maintained by vitamin D and PTH. The required calcium intake for individuals of different ages and gender should be between 400 and 1200 mg.<sup>8</sup> But most diet routines of people don't satisfy this. The most common defect due to low intake of calcium is osteoporosis which compromises bone health, and leads to reduced bone mass and fragility, making the bones weaker.<sup>9</sup> Calcium being a mineral contributes to bone mineral density (BMD), and when calcium is lost from bone, the BMD reduces. The key focus is to identify osteopenia early so that calcium supplementation can be given to solve osteopenia before it leads to osteoporosis.<sup>9</sup> Calcium levels are monitored by calciotropic hormones like vitamin D and parathyroid, which control the transport of calcium in the intestine, kidney and bone. Any imbalance in the serum calcium concentrations are detected by the Calcium Sensing Receptor (CaSR) and the parathyroid, therefore inactivating the PTH receptor, and this leads to jumping in the PTH secretion.<sup>10</sup> CCM is one of the most important minerals that a pregnant woman needs as it gives the baby the aid to develop its vital structures like the skeleton. Since calcium is so important to both the mother and growing baby, pregnant women should be given supplements in case their body is not able to cope with the calcium levels and requirements in that vulnerable state.<sup>11</sup> Therefore, monitoring patients after surgery is one of the key steps towards postoperative care, which mainly involves measuring serum calcium levels and taking necessary action in terms of giving vitamin D and/or calcium supplements.<sup>12</sup>

## METHODS

The study was conducted using four databases Google Scholars SAGE, DOAJ and PubMed. The selection of papers was done based on keywords and themes relevant to this review. Further the published papers from these databases were arranged in systematic order with respect to year of publication.

## RESULTS

### Role of CCM in ENT

Many Controlled intervention trials with CCM were performed. A double-blind, placebo-controlled calcium supplementation study has been carried out in children and adolescents.<sup>3</sup> The primary endpoints were time to first myocardial infarction and time to first stroke and the secondary endpoint was time to death.<sup>13</sup> Eleven adults were taken as subjects and upper removable intra-oral slabs were made for each subject. The erosion was measured by the loss of enamel of the casts of the enamel surface. The casts were obtained and compared before and after the exposure to oral fluids. Oral isotope was used to measure Ca absorption in healthy women.<sup>7</sup> The procedure was approved by the Human Subjects Committee at Indiana University. A blind and non-

randomized clinical study was taken into consideration on a group of 100 healthy Indian children.<sup>14</sup> A questionnaire was given including the medical history and juice consumption of the person.

The results obtained were similar in both the cases i.e rats and humans (women). In the first experiment, CCM was compared against CaCO<sub>3</sub>, and in the second, it was compared against milk.<sup>1</sup> It was observed that CCM had higher 6-day retention values. Calcium absorption was significantly better than milk in the case of orange juice beverages.<sup>1</sup> There is a significant effect of pH treatment on the amount of soluble calcium present in ionic form and the total soluble calcium.<sup>4</sup> When the pH is 2.0, all the soluble calcium is present in the ionic state. When the pH increases to 7.0, there is a different solubility pattern for each calcium salt.<sup>4</sup> Both calcium citrate and CCM exhibited higher amounts of soluble calcium complex. At pH 2.0, there was a difference in the soluble calcium levels of all the calcium salt sources. When the pH was increased to 7.0, all the calcium phosphate that was present, precipitated.<sup>4</sup> This unique change in the solubility patterns at different pH describes the importance of pH adjustments during in vitro testing of bioavailability.

Results from double-blind, placebo-controlled calcium studies showed that the absorption rate of milk or calcium carbonate is much lesser than the calcium supplementation or CCM fortified juices.<sup>3</sup> This result also suggested that CCM has also proven to be a bigger help than calcium carbonate to prevent bone loss in older postmenopausal women.<sup>3</sup> It could be observed that total calcium intake in the prepubertal CCM supplemented group is greater than that of the placebo group. On the other hand, increased calcium intake was not associated with the CCM supplemented group, rather it was greater in the placebo group in pubertal subjects.

A calcium citrate malate additive is formulated to curb erosion of soft drinks.<sup>15</sup> Calcium and phosphate supplementation techniques have been a source for a new method to curb erosion. The effectiveness of this additive is measured gravimetrically as the percentage of weight loss. Experiments show that the percentage has been reduced from 8.7% to figures in the range of 0.05% to 0.75%, in the presence of varying concentrations of CCM.<sup>15</sup> Experiments done on a group of rats show that erosive property has been reduced from 4.29±0.85 to 0.95±0.38 and 0.71 ±0.55 by the CCM supplement (recorded on a 0-6 grading scale of increasing severity).<sup>2</sup> Magnesium intake did not differ between the groups and a mean was observed as 176mg/day.<sup>16</sup> Calcium intake was different in low and high calcium groups and the mean was calculated as 667mg/day and 1667mg/day respectively.<sup>16</sup> However, magnesium balance was not affected due to low or high calcium intake and average as 21mg/day.<sup>16</sup> In another experiment conducted, the mean depth of enamel loss was 12.8 µm for the 9 enamel slabs exposed to diet cola compared with 3.8 µm of enamel lost in the 9 enamel slabs exposed to distilled water.<sup>17</sup> This difference of 9.0 µm was



statistically highly significant. There was no difference in depth of loss of enamel between distilled water (5.0  $\mu\text{m}$ ), citric acid-based orange drink CCM (5.2  $\mu\text{m}$ ), and citric acid-based orange drink- CCM (6.1  $\mu\text{m}$ ,  $p < 0.05$ ).<sup>17</sup>

Calcium absorption from calcium carbonate was noted as 27% and that from CCM was noted as 36%.<sup>5</sup> It was concluded that calcium absorption from calcium citrate malate was significantly higher in these children compared to calcium absorption from calcium carbonate.<sup>5</sup> There were 5 patient-level data and 11 with trial-level data eligible for inclusion. In the studies inclined towards patient-level data, 143 people had myocardial infarctions which were allocated to calcium as compared to 111 allocated to placebo.<sup>13</sup> The meta-analysis of trial-level data showed similar results wherein 166 allocated to calcium has myocardial infarction and 130 to placebo.<sup>13</sup>

The adequate intake of calcium is important for the systematic and full development of bones. An experiment in rodents suggested that the adequate intake of Calcium affects the oral bone surrounding and supporting the teeth, especially alveolar bone.<sup>6</sup> Calcium-fortified food products help in preventing tooth loss and tooth erosion. Consumption of acidic food and beverages harms dental enamel erosion. There have been various studies to prove that CCM reduces dental erosion and reduces the erosive effect of much acidic food products.<sup>17</sup>

#### Role of CCM Post Surgery

After parathyroidectomy surgery, it is insisted that patients are observed primarily for calcium levels. In many cases, it was seen that a drop in calcium levels in serum occurred on the first day after surgery and lasted for some time after that. Over the years, parathyroidectomy has evolved into a minimally invasive procedure that can now be completed within 20 minutes for most patients, as it requires smaller dissections and lesser anaesthesia. A study shows that in 1997, 80% of patients were sent home immediately after surgery and by 2003, 100% were sent home except for a few rare and complex cases.<sup>18</sup> But, here there was a problem, the drop in serum calcium levels post-surgery was not accounted for and these patients dealt with complications like hypocalcaemia and definitely required supplements.<sup>18</sup>

Thyroidectomy surgery has been proven to be a safe technique. However, it does have one complication post-surgery, which is that of hypocalcaemia and this is the only reason that patients are kept under observation and not discharged early. Usually, patients are all given supplements after thyroidectomy as there are calcium losses. These losses can be temporary and can revert back faster in some cases, and giving supplements might cause more harm than good in these scenarios. Therefore, it is a new finding that it is better to check PTH levels on the day of thyroidectomy and along with the calcium levels, during discharge and before giving calcium supplements.<sup>19</sup>

People suffering from obesity usually go in for surgeries that involve a bypass that can lead to a huge loss of

nutrients and this, in turn, results in complications. A decrease in calcium and vitamin D levels compromises bone health as it increases parathyroid hormone in the body, this condition is called secondary hyperparathyroidism. Secondary refers to a negative calcium balance that increases PTH (parathyroid hormone) levels, along with bone defects like osteopenia or osteoporosis.<sup>20</sup> Most protocols take into account the calcium (and now PTH) levels after surgery, but there would be a marked benefit seen in case pre-and post-operative supplementation was done.<sup>21</sup>

The comparison of the effects of Calcium carbonate and calcium citrate are directly done on calcium regulating hormones and marker of bone resorption in postmenopausal women that usually have a low intake of calcium and bone density. 40 postmenopausal women, for 12 weeks, were randomly administered 1000mg/day of calcium carbonate or calcium citrate with their meals.<sup>22</sup> After this time period, these women went through a 2 week washout time period without calcium supplements and after which they underwent a 12 week time period with alternate calcium supplements. Postmenopausal women with any disease or injuries related to bone health were not picked for this study as it would hamper the process.<sup>22</sup> Out of the 40 chosen women, 34 women completed the study as 6 were either not eligible or were withdrawn. Over the due course of the study, these women were evaluated for markers of bone resorptions, ionized calcium, PTH and urinary calcium excretion. In this time, the effect of Calcium Citrate was found to result in the decrease of all four markers of bone resorption the markers being NTX, CTX, Dpyr and sNTX.<sup>22</sup> This decrease did not occur with Calcium Carbonate. Calcium Citrate and Carbonate: Calcium Citrate had better bioavailability in 25 postmenopausal women, depicted by an increase in serum and urinary calcium levels, and PTH levels.<sup>22</sup> The reason for calcium citrate being more bioavailable when had with a meal is that it has a low gastric acid output since carbonate requires an acidic environment for absorption. Calcium carbonate does not work in patients that have achlorhydria, and here calcium citrate was significantly better. In the case of proton pump inhibitors and H2 blockers decrease acidity thereby making it difficult for carbonate to work. In terms of cost-benefit, calcium carbonate had the advantage.

A total of 6000 patients were taken for the study over a period of 4 years. All patients were ones suffering from primary hyperparathyroidism, and had parathyroidectomy surgery and were also discharged after about 2.5 hours. 3/4th of the population were women, and the remaining 1/4th were men.<sup>18</sup> The average age was 59.8 years and the ages ranged from 14-95 years. Patients were divided into groups based on their average calcium levels before surgery. Every patient of a group was given the same number of calcium supplement tablets (each having 315 mg of calcium citrate and 200IU vitamin D-3).<sup>18</sup> It is a controlled study with high doses given immediately post-surgery and then the amount tapers towards the next two



weeks. The first dose should be administered within 3 hours post-surgery.<sup>18</sup> Out of 6000 patients, 7 patients had severe complications and needed intravenous calcium, between days 3 and 5 post-surgery. Also, 5 out of these 7 had a case of 4-gland hyperplasia and underwent parathyroidectomy needed IV calcium, while only the other 2 with adenomas required IV calcium.<sup>18</sup> The most common symptoms of hypocalcaemia in these patients included hand tingling and paraesthesia, mental fog and hand cramping. Every patient was given 10 pills maximum per day, and if the need arose, then they were given 2 more every 2 hours, but no one would be given more than 10 pills in the 24-hour period without asking the surgeon.<sup>18</sup>

A study conducted in Christian Medical College Hospital in Vellore took into consideration 125 patients who had undergone thyroidectomy. The difference in hypocalcaemia between low and high PTH was that of 25%.<sup>12</sup> After the surgery, patients were observed for any complications such as haemorrhage, voice changes and any symptoms of hypocalcaemia. Samples taken to estimate total calcium in serum, albumin and PTH levels were done by 6 AM on the day that followed the surgery (no exceptions). Low serum calcium concentration gave an indication of hypocalcaemia, but they also measured serum magnesium, to check if the hypocalcaemia was severe or resistant to calcium and vitamin D therapy.<sup>12</sup>

A study was conducted on 20 patients with prior consent to be included in the study. Patients who had other comorbidities and medications that affect bone health were excluded. Choosing patients for the study was by conducting biochemical tests that showed any abnormalities in the alkaline phosphatase, vitamin D and/or PTH levels.<sup>20</sup> However, during statistical analysis and data tabulation, their age, body mass index, serum calcium levels were also taken into account. Patients were put in 2 separate groups- one treated with calcium citrate (600mg) with 400IU of vitamin D, given twice every day for 2 months; The other group was given calcium carbonate (600mg), with the same amounts of vitamin D, for the same duration.<sup>20</sup>

### CCM in Gynaecology

Earlier, there were doubts about the effectiveness of calcium supplementation in improving bone density reduction in postmenopausal women and many contrasting evidences were found. A study had previously indicated that the rate of bone loss was higher in women who had a calcium intake under 400 mg per day.<sup>24</sup> Thus the subjects of this study were divided into two groups: the first group with daily calcium intake under 400 mg, and the second group with daily calcium intake above 400 mg. Further considering the fact that women closer to menopause (5 years or less) had a higher rate of bone loss compared to women who had menopause more than 5 years ago, the trial was divided into two phases, with early postmenopausal and late postmenopausal women.<sup>24</sup> In this two-year-long double-blind, placebo-controlled randomized trial, each category was subdivided into three

groups: one received placebo tablets (microcrystalline cellulose), or 500 mg doses of either calcium carbonate or calcium citrate malate.<sup>24</sup> The early-postmenopausal women had a major decrease in bone density at the spine after 2 years of the study, regardless of their calcium intake. The femoral neck and the radius bone density did not change significantly. In the late- postmenopausal women with low dietary calcium intake, the ones who received calcium citrate malate showed no significant size of bone loss at any site.<sup>24</sup> The bone density of the spine decreased in both the calcium carbonate and placebo group, and the bone density of the femoral neck significantly decreased only in the placebo group. In the women with higher dietary calcium intake, the treatment didn't lead to any sort of change at any site. It was ultimately concluded that late postmenopausal women with low dietary calcium intake benefit the most from calcium supplementation.<sup>24</sup>

It has been established that bone density increases rapidly during puberty and the highest bone density at hip and spine of females is achieved by 20 years of age, the study was carried out to study the effect of calcium supplementation on the overall bone mineral content in adolescent girls. A total of 94 premenarchal girls with a mean age of  $11.9 \pm 0.5$  years participating in the study were randomly divided into two groups during the 18-month course of the trial: one group received placebo tablets and the other received 250 mg calcium citrate malate (6:2:3).<sup>25</sup> The dietary calcium intake of the groups did not differ. After 18 months, the mean height, weight, BMI and body fat percentage of both groups did not differ. Trends were the same for urinary gonadotropin, estradiol, testosterone and Integrated Estrogen Exposure score. The bone mineral density and bone mineral content, both overall and site-specific, showed a great increase in the supplemented group as compared to the placebo group.<sup>25</sup> Urinary calcium excretion was also higher in the supplemented group.<sup>25</sup> Thus, in conclusion, a modest increase in calcium intake via supplementation can help increase peak bone mass and avoid the possibility of osteoporotic fractures in future.

A double-blind, placebo-controlled 2 year-long trial was carried out to study the role of essential trace elements copper, zinc and manganese, in combination with or without supplemental calcium on spinal bone loss in older women.<sup>26</sup> 59 out of the total 120 participants completed the study. Among other reasons, 21 subjects dropped out of the study due to adverse side effects including gastrointestinal issues such as nausea, gas and indigestion, which were believed to be caused by supplements. The subjects were divided into four groups of study: one receiving only placebo tablets, the second receiving only active trace minerals, the third receiving only active calcium and the fourth receiving both active trace minerals and active calcium. Active calcium was given in the form of calcium citrate malate (ratio 6:2:3, 1000mg/ day). Active mineral tablets consisted of 15mg Zinc, 5mg Manganese and 2.5mg Copper.<sup>26</sup> At the end of the 2-year course of the trial, the greatest decline in bone mineral density was seen



in the group receiving placebo tablets ( $-3.53 \pm 1.24$ ), the decline was relatively less in the group receiving only trace minerals ( $-1.89 \pm 1.40$ ) and even better in the group receiving only calcium supplements ( $-1.25 \pm 1.46$ ).<sup>26</sup> The best results were obtained in the group receiving both active calcium and active trace minerals; there was no loss in bone mineral density, rather there was a net gain of  $1.48 \pm 1.40$ .<sup>26</sup> This established that trace minerals, alongside calcium supplementation, are also important for improving and maintaining a healthy bone mineral density.

Other than bone mass and density, bone area and geometry could be equally important variables due to their role in bone strength. Thus, the primary aim of this calcium intervention trial was to analyse the effect on the bone area and bone density. For this study, 112 Caucasian premenarchal girls with a mean age of  $11.9 \pm 0.5$  years were shortlisted, 21 of which eventually dropped out at a regular rate throughout 24 months of this study.<sup>27</sup> These participants were divided into two groups: one group received placebo tablets (microcrystalline cellulose) and the other received 250mg CCM tablets (6:2:3 molar ratio).<sup>27</sup> To control the role of genetic variation in average BMI and initial bone density, the groups were divided by stratified randomization into two groups with balanced baseline values of BMI and LSBMD. At the end of the 2-year span, both groups showed normal growth and pubertal progression. Bone acquisition levels were higher in the calcium supplemented group than in the placebo group.<sup>27</sup> There was a 12-24% difference in the increases in the lumbar spine and pelvis bone measurements in supplemented groups as compared to the placebo group.<sup>27</sup> To further understand the role of estrogen in bone gain, Tanner score and IEES were both compared with TB BMD.<sup>27</sup> Even though IEES did not yield clear results when participants were subdivided into groups according to below- and above-median values for Tanner score and below- and above-median values for dietary calcium intake, the association between the two was significant. It was found that only the girls with above-median values of Tanner score benefited from calcium supplementation and had greater gains in TB BMD, the girls with below-median scores on the other hand showed no major effect of supplementation.<sup>27</sup>

Epidemiological studies have been both in favour of and against the effectiveness of calcium supplementation. Positive results have been efficiently obtained with much difficulty as some factors like multifactorial nature of osteoporosis, variable absorption of calcium, dietary calcium deficiency, unique biochemistry of postmenopausal women and readjustment of bone mass due to varying hormones (in both sexes) hinder the outcomes.<sup>28</sup> The majority of studies indicate that calcium supplementation cannot stop postmenopausal bone loss.<sup>28</sup>

Adolescents and the effect of calcium supplementation on their bone mass gain and accretion have been widely analysed. A study of 11-12-year-old adolescent females to

analyse the effect of calcium supplementation showed an average increase of 24 grams of bone per year in the supplemented group.<sup>28</sup> If this trend was kept up for 30 years, the peak bone mass would have significant protection from postmenopausal bone loss. In another study in 45 pairs of pre-pubertal identical twins, one twin was given 700mg of CCM supplement.<sup>28</sup> Thus one twin had a daily intake of  $1370 \pm 303$  mg while the other had  $888 \pm 173$  mg. There was a significant gain in bone mass in the supplemented twins.<sup>28</sup> Similar trials have been performed on adolescent girls who were divided into three groups receiving placebo or 500mg/day or 1000mg/day elemental calcium as CCM. The first two groups did not have a significant bone mass gain but the group 1000mg/day had an average skeletal mass gain of  $29 \pm 7$  gm. These results were, however, obtained at a daily calcium intake of  $1618 \pm 288$  mg which sheds light on the need to re-evaluate the recommended intake.<sup>28</sup>

Many studies have established that pre-and postmenopausal women benefit from calcium supplementation more than menopausal women. In Hugh-Dawson study with postmenopausal women, it was clear that none of the calcium supplements could prevent bone loss in menopausal women but in late postmenopausal women, CCM showed a 60-per cent reduction in spinal bone loss, which was a lot better than placebo and even calcium carbonate supplements (only 15 per cent reduction).<sup>28</sup> Better absorption of calcium citrate malate was demonstrated by an increase in urinary calcium in women with lower dietary intake. Later studies that used higher levels of calcium supplementation were unable to halt spinal bone loss at doses as high as 2500mg/day.<sup>28</sup> This points towards the importance of trace minerals (TMIN) such as copper, zinc and manganese. Thus, postmenopausal women were categorised as estrogen using and non-estrogen using groups and were given an only placebo, only TMIN, only CCM or CCM plus TMIN.<sup>28</sup> No differences in bone mass were noticed in estrogen using women, but in non-estrogen using groups, the greatest decline in bone mineral density was seen in the placebo group, then in the TMIN group and the least decline was in the CCM group. Additionally, in the CCM plus TMIN group, there was no decline, rather there was a slight gain in bone mineral density.<sup>28</sup> The effect of the combination of CCM and vitamin D in postmenopausal women living at 42-degree latitudes was also studied. They are unable to manufacture vitamin D during the winter months. The group receiving vitamin D and CCM showed an increase in bone mineral density, while the other groups had a net decrease.<sup>28</sup>

Insufficient dietary intake of calcium and vitamin D is a primary concern because when calcium or vitamin D is lower in the body, calcium homeostasis is maintained by parathyroid hormone at the expense of bone.<sup>29</sup> Thus lack of calcium accumulation negatively impacts peak bone mass. Many studies have shown that increasing dietary calcium intake up to 1200-1600 mg/day has positive effects on bone acquisition.<sup>29</sup> In a study with subjects aged



7-17 years, the group of subjects with higher calcium intake had 1.6-5.1% higher bone density than the control group.<sup>29</sup> Similar results were obtained in a co-twin placebo-controlled trial where there was a 3.7% difference in TBBMC when one consumed a more calcium-rich diet than the other. Vitamin D deficiency leads to decreased calcium absorption which is a prime cause of bone abnormalities and rickets due to defective mineralization and altered growth plate formation.<sup>29</sup> Studies have also related vitamin D deficiency with a rise in parathyroid hormone levels. Vitamin D receptor is important in all calcium-regulated tissues as it is in ovarian function. Vitamin D deficient mice were less fertile compared to replete littermates. It has even led to uterine hypoplasia and impaired folliculogenesis, alongside low levels of estradiol and higher LH and FSH.<sup>29</sup> VDR-null mutant mice showed decreased gene expression as well as lower activity of estrogen synthase or aromatase; estrogen supplementation increased uterine weight in these mice and normalised histological abnormalities. Calcium supplementation in VDR- null mice corrected low serum levels, and more importantly, improved CYP19 gene (encodes P450 of aromatase) expression to 20% and aromatase cytochrome 450 activity up to 60% of the normal.<sup>29</sup> Thus calcium and vitamin D have a key role in estrogen biosynthesis and normal aromatase gene expression.

Postmenopausal women are at a greater risk of obesity due to reduced circulating sex hormones and metabolism disbalance due to the absence of the menstrual cycle. Calcium and Vitamin D supplementation have proven benefits in improving body composition: high calcium intake is associated with high-fat oxidation and increased satiety; improved vitamin D signaling enhances expression of lipolytic and thermogenic genes in adipose tissue.<sup>30</sup> A preclinical trial also reported that higher dairy calcium intake and higher serum vitamin D levels are associated with greater diet-induced weight loss, and as reported in another study they may even facilitate weight loss. Contrasting evidence has given rise to another possibility that dairy calcium has this effect due to other bioactive compounds present in dairy working in unison with calcium. This was a randomized, parallel armed study carried out in 128 subjects to identify the impact of calcium supplementation (with or without vitamin D) on different groups of women having different diet regimes but having exercise training regimes for 14 weeks.<sup>30</sup> There were three groups divided based on the assigned diet regime:

- (1) No dietary modification or CTL group
- (2) Low-calorie high- protein or LCHP diet group
- (3) low-calorie high-carbohydrate or LCHC diet group.

Each of the diet based groups was subdivided into three categories which were given either:

- (1) 800 mg of elemental calcium as calcium carbonate (Ca),

- (2) 800mg calcium (calcium tetrahydrate + calcium malate) with 400 IU/day of vitamin D, 300 mg of magnesium, 7.5 mg of zinc, 2 mg of copper and 2 mg of manganese (Ca+D)
- (3) maltodextrin placebo.

Analyses at the end of the 14-week intervention showed a major decline in resting energy expenditure by 80 kcal/day. This decrease was greater in the Ca+D group during the weight-loss intervention but not in comparison to total body weight. LCHC and LCHP, both groups experienced great fat loss, this loss was greater in the Ca+D subcategory compared to Ca supplemented subcategory in the LCHC group.<sup>30</sup> Supplementation showed no effect on weight loss in the LCHF diet group. Thus calcium supplementation benefits people having a hypo energetic diet during weight loss. Finally, supplementing calcium supplementation with vitamin D does not have any major benefit with weight loss compared to only calcium supplementation.<sup>30</sup>

### Role of CCM in Orthopedics

Calcium is under close homeostatic control with cycles like assimilation, discharge, and emission and capacity in bone being engaged with keeping up with the grouping of ionized Ca in the plasma inside a firmly managed range.<sup>31</sup> This tight guideline of plasma Ca focus is accomplished through a complex physiological framework containing the association of the calcitropic chemicals, like parathyroid chemical (PTH), 1,25 dihydroxycholecalciferol (1,25 (OH)2D3), and calcitonin, with explicit objective tissues (kidney, bone, and digestive tract) which serve to increment or to diminish the section of Ca into the extracellular space.<sup>31</sup>

Investigations of Ca supplementation in postmenopausal ladies, commonly of one to two years, have shown that Ca forestall bone misfortune can decrease the pace of bone misfortune partly. These investigations uncover that the viability of Ca fluctuates by skeletal site, by menopausal age, and with common Ca admissions of the examination subjects.<sup>31</sup> In an examination researching, caffeine consumption in 489 ladies matured 66 – 77 years, there was a positive relationship between caffeine admission and bone loss. Bone misfortune at the spine was more prominent in ladies devouring 300 mg of caffeine each day than in ladies burning through 300 mg/d.<sup>32</sup> Ladies with the tt hereditary variation of VDR had fundamentally more noteworthy deficiency of bone at the spine than ladies with the TT hereditary variation when their admission was 300 mg/d.<sup>32</sup> The most widely recognized types of calcium accessible to the buyer are calcium carbonate and calcium citrate. Different types of calcium incorporate lactate, gluconate, bone feast, and hydroxyapatite. Calcium supplements are accessible as containers, tablets, bites, wafers, powders, and fluids.

Calcium citrate malate is portrayed as a metastable complex of calcium, citrate, and malate or as a combination of calcium salts involving the calcium salt of citrus extract and malic corrosive.<sup>5</sup> The metastable materials have more than one glasslike state, reflected by



the presence of various hydration states. Calcium citrate malate is depicted as containing between 20 – 24 % of calcium on a dry premise having a pH of 4.0 – 8.0.<sup>5</sup> Hefty metal degrees of under 20 mg/kg are proposed, for lead two solicitors propose a most extreme degree of 2 mg/kg and two others propose a limit of 10 mg/kg.<sup>33</sup> The impact of calcium supplementation on skeletal advancement in four gatherings of 14 C/D female rodents controlled for 4 or 12 weeks as calcium citrate malate.<sup>5</sup>

Customary ingestion of satisfactory calcium (Ca), especially via utilization of food varieties normally high in Ca, requires a conscious way to deal with adjusted nourishment for an enormous number of individuals. Ordinary openness to an inexorably wide assortment of engaging food and refreshment decisions can redirect the accentuation and inclination from innately Ca-rich food sources that very frequently are to a great extent under-consumed by those most needing them.<sup>33</sup> Under particular conditions, like lactose narrow-mindedness, hypersensitivities, severe vegetarianism, and individual abhorrences, dairy food varieties are not considered as a feasible choice or are burned-through in deficient amounts to meet Ca prerequisites by numerous subgroups.<sup>33</sup>

The Food and Drug Administration (FDA) is altering its marking guideline approving a wellbeing guarantee on the connection among calcium and a decreased danger of osteoporosis to incorporate nutrient D so that, notwithstanding the case for calcium and osteoporosis, an extra case can be made for calcium and nutrient D and osteoporosis; dispense with the prerequisite that the case list sex, race, and age as explicit danger factors for the advancement of osteoporosis; dispose of the necessity that the case doesn't state or infer that the danger of osteoporosis is similarly material to the overall U.S. populace, and that the case distinguish the populaces at specific danger for the improvement of osteoporosis; wipe out the necessity that the case recognize the component by which calcium diminishes the danger of osteoporosis and rather make it discretionary; dispose of the prerequisite that the case incorporate an articulation that a complete dietary admission more noteworthy than 200% of the suggested every day consumption (2,000 milligrams (mg) of calcium) has no further advantage to bone wellbeing when the food contains 400 mg or a greater amount of calcium per reference sum usually devoured or per all out day by day suggested supplement admission; and permit reference for the need of active work in both of the wellbeing professions to be discretionary rather than required.<sup>34</sup>

Ca assimilation happen prevalently in the jejunum and the ileum and colon. Take-up happens by dynamic vehicle and basic aloof dispersion.<sup>35</sup> At low Ca admissions dynamic vehicle prevails, however as admissions increment more is consumed by vague pathways.<sup>35</sup> The metabolite of nutrient D (1,25-dihydroxycholecalciferol) animates Ca transport across the intestinal cells by inciting the creation of a Ca-restricting protein.<sup>35</sup> This cycle happens inside the

villus cells through the ordinary interaction of receptor restricting, DNA communication, and courier RNA creation. Thus, nutrient D is basic for powerful Ca ingestion.<sup>35</sup>

Around 97% of the sifted Ca load is re-consumed by the renal tubules and the leftover 3%, which is discharged in pee, addresses the mandatory misfortune.<sup>35</sup> The significant determinant of urinary Ca discharge is dietary Ca admission. Urinary Ca discharge is higher when protein and Na admissions are high than when admissions of these two supplements are low.<sup>35</sup>

Intense oral calcium load showed, through the concurrent expansion in serum calcium and urinary calcium discharge, that the bioavailability of the marine calcium sources is as great (Phoscalim) or better (Glycollagen) as a similar admission of dairy calcium from milk.<sup>36</sup> Besides, the marine calcium load actuated a more prominent diminishing of iPTH in the Glycollagen bunch than milk and a more noteworthy lessening in bone resorption reflected by s-CTX, since Phoscalim has an almost comparable impact on serum PTH than milk and a lesser impact on s-CTX than milk.<sup>36</sup>

This examination was intended to decide if a was diminished in kids with CF and to build up impacts of calcium and nutrient D3 supplementation on a. Likewise, it was intended to decide if expanded dietary enhancements of nutrient D3 and calcium would further develop serum minerals, markers of bone turnover, and estimations of bone mineral substance (BMC) in these kids. Subjects were enlisted from the Cystic Fibrosis Clinic at the University of Missouri. The Institutional Review Board of the School of Medicine supported the investigation and all guardians gave composed assent with all kids more than seven giving consent. Kids somewhere in the range of 3 and 15 years were qualified, the two guys and females. Kids stayed on their standard drugs, which included pancreatic compounds and generally ADEK nutrients containing another 400 IUD. Kids on oral or intravenous glucocorticoids were avoided. Leather treater Staging utilizing a self-distinguished picture framework was done toward the start of each stage. The significance of Ca supplementation for bone wellbeing is grounded and, along with nutrient D, is considered as a vital part of any preventive or restorative routine for osteoporosis.<sup>37</sup> The gainful impact of long haul Ca and nutrient D supplementation on bone and break hazard in old ladies has additionally been recorded in a few clinical preliminaries.<sup>37</sup>

Bioavailability in the gut and for bone is the initial standard to consider while choosing a Ca salt.<sup>38</sup> Great intestinal absorbability is required, yet it is just the first step in quite a while of bioavailability for both bone mineral growth and bone misfortune avoidance, especially in the old. Some dietary variables impact bone Ca accumulation and additionally resorption, just as urinary, Ca discharge. Accordingly, this load of components will decide the general bioavailability of different Ca salts. The worth of



advantageous Ca and nutrient D in bone wellbeing is grounded, there is an unmistakable absence of agreement in regards to different nutrients and minerals embroiled in bone wellbeing.<sup>38</sup> Ca and nutrient D supplementation is suggested in postmenopausal ladies and the old, and instances of osteoporosis. Calcium lysine doesn't ionize in the gut, in this manner wiping out the possibility to meddle with iron ingestion. L-lysine can both upgrade intestinal Ca assimilation and work on the renal protection of the retained Ca.<sup>38</sup> The consolidated impacts might add to a positive Ca balance, subsequently recommending the likely convenience of L-lysine supplements for both preventive and remedial intercessions in osteoporosis.<sup>38</sup>

## DISCUSSION

Calcium is the fifth most abundant mineral in our body. Calcium supplementation plays a vital role in maintaining bone health throughout life. There is a difference in the retention values in both A and B experiments in rats. Younger animals absorb better and have higher turnover. Both factors elevate retention. The results from the CCM supplemental group provide evidence that there has to be an increase in the calcium intake above RDA (Recommended Dietary Allowance) to optimize bone mass acquisition during childhood and adolescence.

With the increasing use of soft drinks, especially in adolescent groups, there is a growing concern in the dental sector. The problem is that product reformulation is not a simple matter and many suggested additives can have adverse effects. It is necessary to keep in mind that acids also have a preservative effect so if there is any reduction in acidity levels, it should be observed.<sup>17</sup> This study reflects chronic magnesium utilization and not acute responses to the increase in calcium diet. There were several limitations in the study conclusions. It can be possible that the effect of calcium on magnesium utilization takes place gradually and not immediately in a period of 14 days. Calcium intake does not influence magnesium utilization.<sup>16</sup>

Although the enamel slab is a well-known system, its usage as an experimental erosion system was new. The palatal area of the maxillary anterior teeth is the surface that is most exposed and affected by erosion. There was a loss of enamel, to some extent, when exposed to distilled water. It may be caused by erosion during the 6 days and nights of intra- oral use. There are two ways to design these experiments.

1) leaving the slabs in the mouth all of the time and rinsing with the test solution. This method measures the real-life situation.

2) insert the slabs into test solutions out of the mouth before putting the appliance back into the mouth. This method allows the comparison between two solutions which helps in controlling and reducing the experimental variations.<sup>16</sup>

Calcium from CCM is more bioavailable, around 8-15% than from other sources of calcium.<sup>5</sup> This does not affect

the safety of use in the long term, supplementation studies show that CCM is well tolerated by humans. For many people around the globe, the adequate intake of calcium is quite low. This is a major health problem and is getting worse day by day. People are attracted to food products that have acidic effects without even knowing their downfalls. Calcium-fortified food products must be palatable to the extent that their taste and texture are not affected. The cost of habitually purchasing good quality Ca-fortified foods and supplements is negligible compared to the exorbitant costs associated with substandard nutrition and the resulting pathologies.<sup>6</sup> From the experiments conducted, it can be concluded very clearly that calcium supplements are linked with an increased risk of myocardial infarction and cardiovascular disease. As calcium supplements are in great demand nowadays, these risks can turn into a big burden on the world population.

Calcium absorption has to vary differently in healthy adult humans as they have their normal self-selected diets having different Ca sources. The conclusions were limited due to the use of two different groups of women. Although they were from the same age group and in the same geography, there was not enough information regarding their vitamin D status or self-selected dietary intake. Calcium fortification is an important aspect for increasing the calcium intake in people especially those who are lactose intolerant. The most effective way to prevent the loss of tooth minerals is the modification of beverages with the fortification of calcium. The effect of calcium fortification on oral pH changes and taste perception should be evaluated in further studies.

Doctors are still unsure of the safety of the parathyroidectomy since hypocalcaemia occurs anytime past the second day after surgery and patients go into complications if precautions are not taken. Every patient must comply with the calcium supplementation therapy immediately post-surgery, irrespective of how successful the surgery was or what their serum levels were. This gives a broader range of control over the post-operative measures and can keep any unwanted things coming the patient's way in check.

Usual therapy for patients with end-stage renal disease due to other morbidities is to put them on calcium supplements with activated vitamin D (calcitriol or its analogues). Many go with calcium carbonate since it is more cost-effective, but in cases where there are antacids in the medication that the patients take, it is difficult to see the real effectiveness of calcium carbonate. In fact, in general, calcium carbonate has about 40% calcium content, while calcium citrate has only a meagre 21.1%. But since calcium citrate does not require an acid environment and due to much higher bioavailability, it tends to have a significantly greater effect on lowering PTH levels. In this case study, calcium citrate was used for a very short time to accelerate the calcium deposition into the bone post-surgery.





This research should be extended to patients with other morbidities and also the interactions of these calcium supplements must be studied so that there are no side effects to this on top of the existing complications. Doctors should take note and observe what calcium levels are, before, during and after the surgery. But sometimes, the calcium levels after surgery might drop later and thus there is a need for preventive measures so that the hypocalcaemia even if it comes, will be mild and well within handleable limits.

The upper limit for a single dose is 500 mg, and it was seen that only doses below this limit gave the highest rates of absorption of calcium. The dose of calcium had a direct effect on the PTH levels, the higher the dose, the lower the PTH, thus it proved vital in eradicating bone defects and also secondary hyperparathyroidism. The greater bioavailability of CCM is due to the fact that malate and citrate are easily ionized, hence their increased absorption rates. Citrate and malate ions are absorbed usually in the upper digestive tract. There have also been studies done on single and double stable isotopes, and it was found that the stable isotopes are  $^{44}\text{Ca}$  and  $^{42}\text{Ca}$ , which were found in serum and urine. It was also understood through tracer as well as varied molar ratios, that CCM absorption exceeds that of the calcium absorbed from various dietary intakes and other calcium supplements. Although it is fair to note that calcium lysinate might change this due to its chelated nature.

The latest development in the field of calcium supplementation after surgeries is because PTH levels are a stronger indicator when measured alongside calcium, and this adds to the efficiency of the process post-operation. Further research can be done based on this as this can be a very good foundation in terms of the accuracy of the result as well as having an added bonus of being a randomized trial. Key experiments done could be extensions of these into a larger group of people including some patients with certain pre-existing defects or medications.

Coming to vitamin D along with calcium supplements, it was also seen that the use of Vitamin D along with the calcium administered resulted in higher levels of calcium in the patients' bodies and reduced risk for them. Hence, postoperative early administration of Vitamin D or Calcium supplements or both together showed higher chances for the patient to not be hypocalcaemic. Unfortunately, the study of pre-operative administration of Calcium and Vitamin D supplements has not resulted in any solid evidence and has been seen to have many limitations.

A new form of calcium supplementation that might change the scenario is that of calcium lysinate, which has the advantage of the fact that L-lysine has a role in enhancing calcium absorption from the intestine as well as in improving renal conservation of absorbed calcium. Thus, proving useful in both prevention and also curing of osteoporosis. In today's world, there's always a concern on how long someone is at the hospital and how much it

would cost to do a treatment. But there is never a perspective that revolves around how meagre the cost of taking up treatment is compared to paying to fix the complications. By giving patients the necessary supplements, based on their postoperative calcium concentrations in their serum, their stay at the hospital is minimized. Yes, there is no doubt that their operative costs will go up, but definitely no complications, and that would mean no return to the hospital after this. A combination of calcitriol and calcium seems to be less expensive as they work with most patients, and patient's bodies too comply with this combined supplementation in most cases. This is because many calcium supplements are selective and they have to dive deep into details of a patient's proton pump characteristics, gastric acid secretions and other drugs that might interact with the supplement. There is a downside to giving all patients supplementation, as that might increase calcium levels, in case a patient actually copes with the calcium loss during surgery. But then again, if monitored properly then it would not cross the maximum limit.

There are upcoming strategies now to supplement based on intact PTH levels and that can be a boon in handling calcium supplementation better.

## CONCLUSION

This research review's purpose is to help the reader understand different aspects posed by the research on the analeptic properties of Calcium Citrate Malate. This is significant because it gives insights into how CCM can be used for the treatment and management of various diseases in different aspects of medicine like gynaecology, orthopaedics and even ENT. It is noteworthy to understand the analeptic properties of CCM post-surgery. There has been much research and discussion conducted on these opinions of the pharmacological properties of CCM. Most of the research found was on the CCM supplementation post-surgery, in menstruating women to combat osteoporosis. More research and testing are required to gain a better understanding of the effective ways in which CCM can be used to treat and manage various other diseases and disorders.

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Not applicable.

## Human and Animal Rights

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**Consent for Publication**

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