CALCIDEF™

Dicalcium Malate 400mg, Vit D2 400 IU, Folic Acid 100mcg, Glycine 10mg Tablets

Calcium with a **DIFFERENCE**

Product Information Brochure

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CALCIUM

Calcium (Ca++) is the most abundant mineral in the body. This essential element is only available to the body through dietary sources.[1] Approximately 1.2 kg (equivalent to about 300 mmol) is contained within the human body, with 99% of this Ca being located within the bones and teeth. Ca is also located in body fluids and soft tissues.[2] It plays a key role in skeletal mineralization, as well as a wide range of biological functions. Over the last 3 to 4 decades, the clinical implications of calcium deficiency are being better recognized, the economic burden of osteoporosis is increasing, and deficiency of vitamin D (important for calcium absorption) is also being documented in tropical countries.[3]

FUNCTIONS OF CALCIUM

Calcium plays a key role in a wide range of biologic functions, either in the form of its free ion or bound complexes. One of the most important functions as bound calcium is in skeletal mineralization. The vast majority of total body calcium (>99%) is present in the skeleton as calcium-phosphate complexes, primarily as hydroxyapatite, which is responsible for much of the material properties of bone. In bone, calcium serves two main purposes: it provides skeletal strength and concurrently, provides a dynamic store to maintain the intra- and extracellular calcium pools.[1]

Calcium is essential for the following

- Formation of bone and teeth
- Muscle contraction
- Normal functioning of many enzymes
- Blood clotting
- Normal heart rhythm

CALCIUM AND BONE HEALTH[4,5]

Bones change in size, shape, and position throughout the life. The two processes that guide these changes are known as modeling and remodeling. Modelling is the process when a bone is formed at one site and broken down in a different site so that its shape and position is changed. Whereas in remodeling, a small amount of bone on the surface of trabeculae or in the interior of the cortex is removed and then replaced at the same site. The remodeling process (Figure 1) does not change the shape of the bone. Remodeling occurs throughout life. Bone remodeling, gives bone its mature structure and maintains normal calcium levels in the body. Destruction, or resorption, of bone by large cells called osteoclasts releases calcium into the bloodstream to meet the body's metabolic needs and simultaneously allows the bone to alter size and shape as it grows to adult proportions. While the osteoclasts resorb bone at various sites, other cells called osteoblasts make new bone to maintain the skeletal structure.

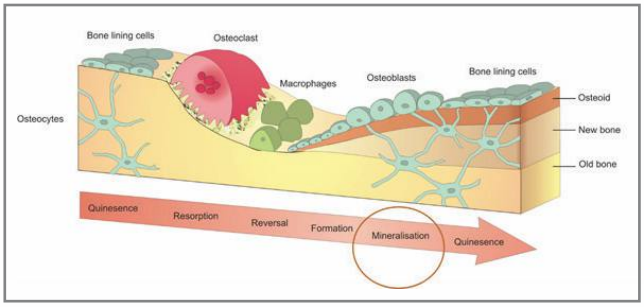

Figure 1. Process of bone remodeling.

The mineralization phase, an important process in remodeling of bone involves precipitation of small crystals containing calcium and phosphate, called hydroxyapatite with collagen matrix (Figure 2). Collagen is made by bone cells and assembled as long thin rods containing three intertwined protein chains, which are then assembled into larger fibers that are strengthened by chemical connections between them, which provides strength to the bony structure.

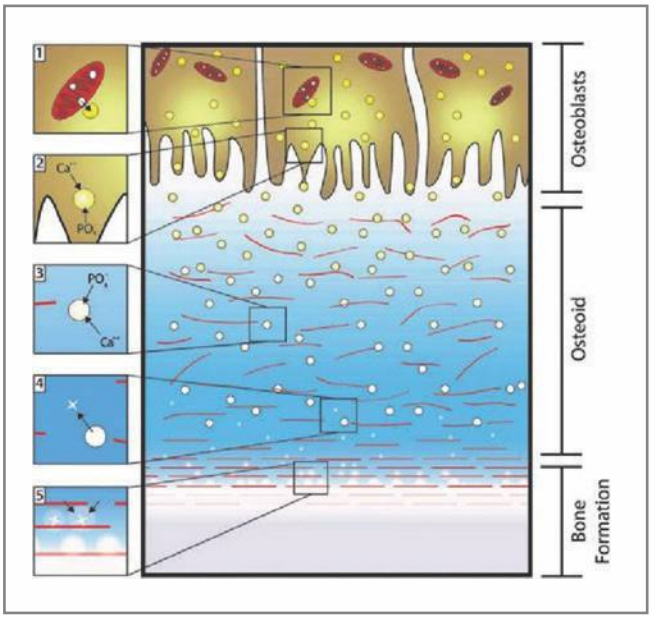

Figure 2. Role of calcium in mineralization of bone.

RELATION BETWEEN INCREASING AGE, BONE MINERAL CONTENT AND CALCIUM:

Age-related bone loss involves a gradual and progressive decline, which is also seen in men. Markedly increased bone resorption leads to the initial fall in bone mineral density. With increasing age, there is also a significant reduction in bone formation.[6] Bone mineral content, provides good estimates of total body calcium. Bone mineral content increases throughout childhood, peaks in adolescence, remains relatively constant in early/late adulthood, and declines in old age. The consistent loss of bone with age is due to inadequate calcium intake, inadequate calcium absorption or excessive excretory loss, or a combination of these problems. Absorption efficiency decreases with age after 40 years at a rate of about 0.21%per year as determined longitudinally in 189 middle aged women. An additional decrease in calcium absorption of 2.2% accompanies the menopause. For women, the combined effect of age and menopause leads to a 20% to 25% decrease in absorption efficiency from age 40 to 60.[7]

CALCIUM REGULATION

Serum calcium is very tightly regulated and does not fluctuate with changes in dietary intakes; the body uses bone tissue as a reservoir for, and source of calcium, to maintain constant concentrations of calcium in blood, muscle, and intercellular fluids.[8] Calcium requirement is regulated by intestinal absorption, renal reabsorption, and bone turnover. These in turn are regulated by interacting hormones, including parathyroid hormone (PTH), 1, 25-dihydroxyvitamin D [1, 25(OH) 2D], ionized calcium itself, and their corresponding receptors in the gut, kidney, and bone. [9]

ABSORPTION

The major site of calcium absorption is the small intestine, where some 90% of calcium is absorbed. Calcium absorption in the large intestine and colon is quite small, probably not exceeding 10% of the total absorbed. Absorption of calcium occurs in the proximal small intestine, both through an

active intracellular vitamin D dependent pathway and through a non-vitamin D dependent paracellular pathway (Figure 3). Calcium absorption proceeds by transcellular and paracellular flux, with the latter accounting for most absorbed calcium when calcium intake is adequate.[10]

The primary regulator of calcium absorption is 1, 25- dihydroxy vitamin D, the hormonally active metabolite of vitamin D, but calcium absorption is also subject to other regulators like, there is evidence that estrogen enhances active calcium absorption. Parathyroid hormone (PTH) acts as a sensor that, in the event of a decrease in calcium levels, stimulates the production of calcitriol, the active metabolite of vitamin D.[11]

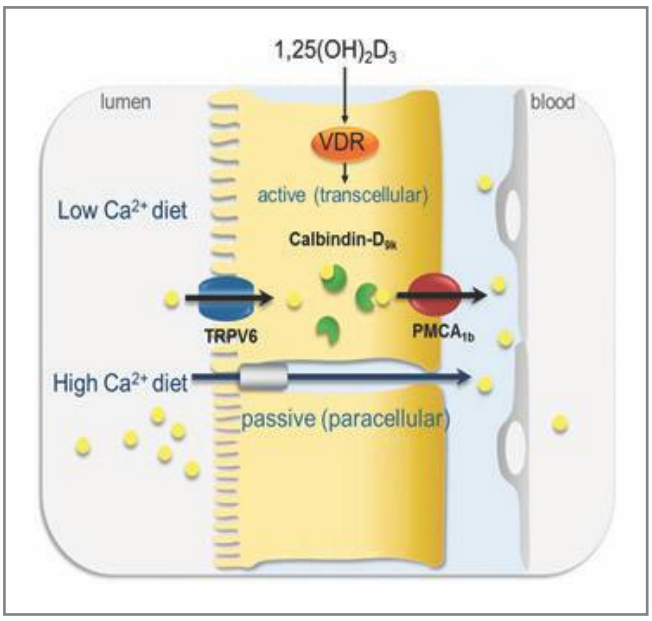

Figure 3. Pathways for absorption of calcium from intestine.

FACTORS AFFECTING ABSORPTION OF CALCIUM

Humans absorb about 30% of the calcium in foods, but this varies depending upon the type of food consumed.[12] Other factors affecting calcium absorption include:

1. Amount consumed: the efficiency of absorption decreases as calcium intake increases.

2. Age and life stage: net calcium absorption is as high as 60% in infants and young children, who need substantial amounts of the mineral to build bone. Absorption decreases to 15%–20% in adulthood (though it is increased during pregnancy) and continues to decrease as people age, recommended calcium intakes are higher for females older than 50 years and for both males and females older than 70 years.[13,14]

3. Vitamin D intake: Vitamin D improves calcium absorption.

4. Phytic acid and oxalic acid in food: Phytic acid and oxalic acid bind to calcium and can inhibit its absorption. Foods with high levels of oxalic acid include Spinach, collard greens, sweet potatoes, rhubarb and beans. Foods high in phytic acid include Fiber-containing whole-grain products and wheat bran, beans, seeds, nuts, and soy isolates

DISTRIBUTION OF CALCIUM

Most of the calcium absorbed is stored in bone as calcium-phosphate complexes, primarily as hydroxyapatite. The non-bone calcium represents <1% of total body calcium (~10 g in an adult) and is responsible for a wide range of essential functions, including extra- and intracellular signaling, nerve impulse transmission, and muscle contraction. Serum calcium ranges from ~8.8 to 10.4 mg/dl (2.2 to 2.6 mM) in healthy subject. This comprises free ions (~51%), protein-bound complexes (~40%), and ionic complexes (~9%).

EXCRETION OF CALCIUM

Calcium is excreted mainly in urine and feces. Calcium excretion in the urine is a function of the balance between the calcium load filtered by the kidneys and the efficiency of reabsorption from the renal tubules. Nearly 98% of filtered calcium (i.e., glomerular filtrate) is reabsorbed by either passive or active processes maintaining neutral calcium balance.

HOMEOSTASIS OF CALCIUM LEVELS.

Serum calcium homeostasis is regulated by a rapid negative feedback hormonal pathway involving the concentration of ionized calcium in serum (Ca, green arrows) and the secretion of parathyroid hormone (PTH, blue arrows) from the parathyroid. A fall in serum calcium (↓Ca) inactivates the calcium receptor in the parathyroid cell (CaR; green circle) and increases PTH secretion (↑↑PTH), which restores serum calcium (↑Ca) by activating the parathyroid receptor (PTHR; blue circles) in bone, to increase calcium resorption, and in kidney, to increase tubular calcium reabsorption. In kidney, PTH secretion augments secretion of 1,25-dihydroxyvitamin D (1,25D; red arrows), which, acting on the vitamin D receptor (VDR, red circles) in gut, increases active calcium absorption and increases calcium resorption in bone.(Figure 4)

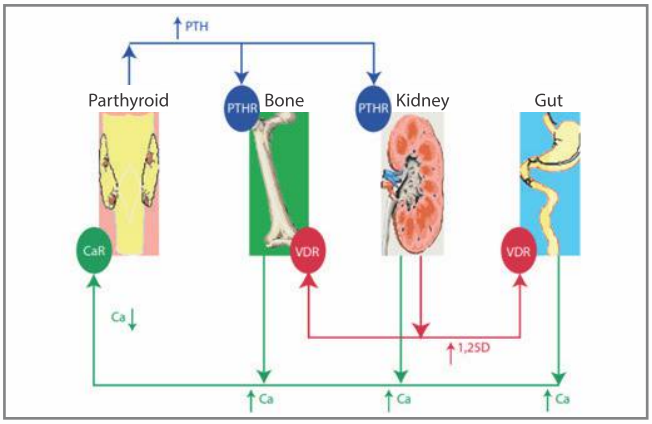

Figure 4. Regulation of calcium.

CALCIUM DEFICIENCY

Both vitamin D and dietary calcium deficiency are highly prevalent in India. Calcium is the most likely to be inadequate in terms of dietary intake.[15] Indian Council of Medical Research (ICMR) recommends 600-800 mg/day of calcium which increases to 1200 mg/day in pregnant and lactating mothers (Table 1). Inadequate intakes of dietary calcium from food and supplements produce no obvious symptoms in the short term.

Over the long term, inadequate calcium intake causes osteopenia which if untreated can lead to osteoporosis. The risk of bone fractures also increases, especially in older individuals. In the largest and longest study reported from India (1963–2005), 52% of the population studied had nutritional bone disease. Osteomalacia (35.3%) and rickets (7.6%) caused by vitamin D deficiency due to inadequate sunlight exposure, dietary calcium deficiency (<300 mg/day) induced osteoporosis, vitamin D and calcium deficiency induced osteoporosis were the commonest disorders. Of the total population studies, about 40.6% had dietary calcium deficiency in critical years of growth. [16]

Calcium deficiency can also cause rickets, though it is more commonly associated with vitamin D deficiency. Calcium intake in the elderly is less than in the young, and reduced absorption efficiency further lowers effective intake.[17]

Table 1: Recommended Dietary Allowances for Calcium[18]

GROUP	PARICULARS	BODY WEIGHT KG	NET ENERGY Kcal/d	CALCIUM mg/d
MEN	Sedentary work	60	2320	600
	Moderate work		2730	
	Heavy work		3490	
WOMEN	Sedentary work	55	1900	600
	Moderate work		2230	
	Heavy work		2850	
	Pregnant woman		+350	1200
	Lactation 0-6 months		+600	1200
	6-12 monhs		+520	

GROUPS AT RISK OF CALCIUM INADEQUACY/ DEFICIENCY[8]

- Postmenopausal women
- Individuals with lactose intolerance or cow's milk allergy
- Vegetarians
- Individuals on a dairy-free diet
- Individuals with a vitamin D deficiency
- Individuals on drugs that can inhibit absorption or increase calcium loss

POSTMENOPAUSAL WOMEN

Menopause leads to bone loss because decreases in estrogen production both increase bone resorption and decrease calcium absorption. At menopause estrogen deficiency impairs the normal cycle by increasing osteoclastic resorption activity without a corresponding increase in osteoblastic activity and the amount of bone resorbed therefore is greater than the amount deposited leading to a net loss of bone.[19] Annual decreases in bone mass of 3%–5% per year frequently occur in the first years of menopause, but the decreases are typically less than 1% per year after age 65.

During the first phase of menopausal bone loss ,women are in marked negative calcium balance. Using total body calcium measurements one can estimate that the average loss of calcium daily in the first 3-4 years is - 200mg daily, this gradually decreases to -45mg daily in years 5—10 post menopause. [19] (Figure 5).

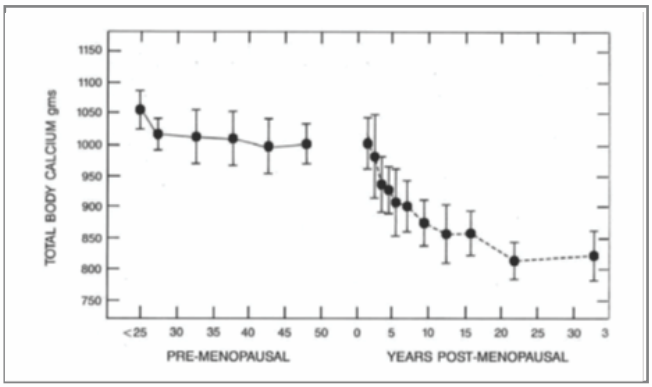

Figure 5. Decline of total body Calcium with years since menopause.

The age related decrease in calcium absorption contributes to further negative calcium balance.

OTHER GROUPS WHO ARE AT RISK OF CALCIUM DEFICIENCY

1. Lactose-intolerant individuals are at risk of calcium inadequacy if they avoid dairy products. Cow's milk allergy is less common than lactose intolerance, affecting 0.6% to 0.9% of the population and are at higher risk of insufficient calcium.

2. Vegetarians: Vegetarians might absorb less calcium than omnivores because they consume more plant products containing oxalic and phytic acids

3. Milk and dairy products are a convenient source of calcium. So Individuals on a dairy-free diet are at increased risk of developing calcium inadequacy.

4. As fractional absorption of calcium is vitamin D dependent, calcium deficiency can occur secondary to vitamin D deficiency.

5. Individuals on drugs that can inhibit absorption or increase calcium loss are also at risk of developing calcium deficiency.

CALCIUM SUPPLEMENTATION

To maintain a normal level of calcium in blood without weakening the bones, people need to consume at least 1,000 to 1,500 milligrams of calcium a day. For optimal bone health, calcium intake must be sufficient to meet the demands of bone mineral accrual and to compensate for losses in feces, urine, and sweat.[20]

In recent years, convincing evidence has emerged with respect to effects of dietary Ca on bone health in all age groups. A meta-analysis of thirty-three studies concluded that there was an overall association between Ca intake and bone mass in premenopausal women. There is considerable evidence that increasing Ca intake above that usually consumed in the diet may have benefits for the development and maintenance of bone, and may reduce the risk of osteoporosis in later life.

CALCIUM SUPPLEMENTS

Calcium supplements are a popular alternative for increasing daily Ca intake. Calcium supplements offer a convenient alternative to women and men unable to consume enough calcium from diet alone.

Calcium supplements come in a wide variety of preparations with different percent of elemental calcium in both liquid and solid formulations (Table 2). The accompanying anions include carbonate, phosphate, sulfate, acetate, lactate, gluconate, glubionate, glycerophosphate, calcium-citrate-malate (CCM), as well as various chelated complexes.[21] There are more than a dozen commonly prescribed calcium supplements and hundreds of different formulations commercially available. Numerous factors need to be considered when selecting a calcium supplements include amount of elemental calcium, bioavailability of calcium, use of H2 blockers or protein-pump inhibitors, number of tablets needed to achieve the desired dose, size of the tablet, form of the calcium, physical properties such as solubility, interference with foods and cost. Medical conditions such as lactose intolerance, impaired gastric acid secretion or achlorhydria and high risk profile for kidney stone formation may impact selection of a calcium supplement.[22,23]

Calcium supplements labels commonly include both the total milligrams of calcium salt and the milligrams of elemental calcium in each tablet. Determination of the dose required to meet daily calcium requirements is based on the amount of elemental calcium.[24]

Table 2: Common calcium supplements and their elemental calcium in percent

SALT	ELEMENTAL CALCIUM IN %
Calcium carbonate	40
Calcium Citrate Malate	21
Calcium Acetate	25
Calcium Phosphates	31-38
Calcium gluconate	9
Calcium lactate	13

The maximum dose of elemental calcium that should be taken at a time is 500 mg. In clinical practice, to obtain optimal clinical outcomes related to calcium supplementation, the dose of calcium should not exceed 500 mg at 1 time. It may be beneficial to supplement in smaller doses 4 times per day to lower PTH levels and decrease bone resorption. Absorption of calcium is greatest when taken in a dose of 500 mg or less.[23]

Calcium Bioavailability: Not only is the calcium content of a preparation significant for providing adequate calcium supplementation for the prophylaxis and therapy of osteoporosis, but also its bioavailability is of essential importance.[25] **Bioavailability, defined here as the percentage of calcium absorbed** from

calcium preparation by human subjects, **depends not only on the intrinsic calcium absorptive capacity of the subjects tested, but also on the calcium absorbability, or the extent to which calcium in given formulation is available for absorption.**[26] Effective absorption and bioavailability are extremely important if significant health benefits are to be derived from supplemental sources of Calcium.[27]

Supplementation with various calcium preparations is now the most common approach to increase calcium intake in individuals concerned with osteoporosis. However, it has been shown that the bioavailability of many commercial calcium preparations are different.[28] The bioavailability of a calcium salt is not proportionate to its solubility, however, and calcium citrate-malate has been shown to be superior in bioavailability to calcium carbonate.

The most common forms of calcium available are calcium carbonate and calcium citrate. Other forms of calcium include lactate, gluconate, and hydroxyapatite.

Calcium carbonate is the most common and least expensive form of calcium. However, for better absorption it has to be taken with meal and can cause GI problems.

Calcium citrate malate is formed from the calcium salt of citric acid and malic acid. Calcium citrate-malate contains about 26% elemental calcium, its bioavailability is as high as 42%, and it also has the most consistently high bioavailability (consistently over 35%) across human studies.[23]

Calcium lactate and calcium gluconate are less concentrated forms of calcium. Calcium lactate contains 13% elemental calcium, whereas calcium gluconate contains only 9% elemental calcium; therefore, these forms are not considered practical for clinical practice.[27]

Albion has developed a new, patented form of calcium, Dicalcium malate. Dicalcium malate was developed as a better alternative to calcium carbonate and other salt forms. Most other calcium forms have much lower elemental calcium content, while Dicalcium malate has 29% elemental calcium.

CALCIDEF

Calcidef is a unique formulation containing dicalcium malate, vitamin D2, Folic acid and glycine. Dicalcium malate is first time introduced in country and is salt of calcium having two moles of calcium and supplies 29% percent of elemental calcium. Vitamin D2 has multiple roles in body along with absorption of calcium from GI tract. Glycine (a non-essential amino acid) and Folic acid (a water soluble vitamin) are believed to have variety of health benefits.

DICALCIUM MALATE

PHARMACOLOGY

Dicalcium Malate is an exclusive form of calcium; it is comprised of 2 moles of calcium attached to one mole of malic acid (Figure 6). Dicalcium malate has 29% elemental calcium.

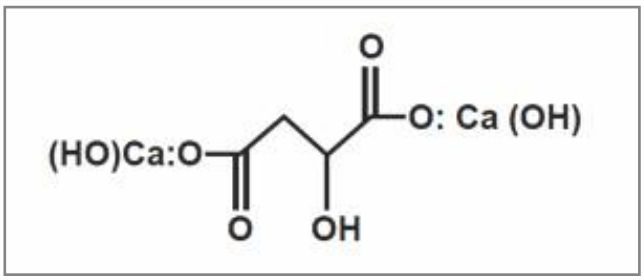

Figure 6. Chemical structure of dicalcium malate.

Dicalcium Malate is 64% malic acid w/w., malic acid is a naturally occurring organic acid found in apples, watermelon, plums, lychees, and cherries in high concentration. **It is more soluble than citric acid** and

forms metal compounds that are of low hygroscopicity allowing for easier storage and better shelf life.

In vitro studies show that Dicalcium Malate, unlike calcium carbonate and some of the other alkali calcium forms does not cause the formation of gas when subjected to stomach acid and does not give rise to acid rebound seen with these other calcium forms. Malic acid is a natural buffering agent. [29]

BUFFERING CAPACITY OF DICALCIUM MALATE

The titration capacity of dicalcium malate and calcium carbonate was compared, by titrating 100 mL of 0.05 M solutions of either dicalcium malate or calcium carbonate with 4N HCl. The pH of each solution was measured with each 0.05 mL addition of HCl.

A comparison of the two titration curves (Figure 7), demonstrated that dicalcium malate has buffering capacity in the gastric pH range; whereas, calcium carbonate has little to no buffering capacity in the gastric pH range.

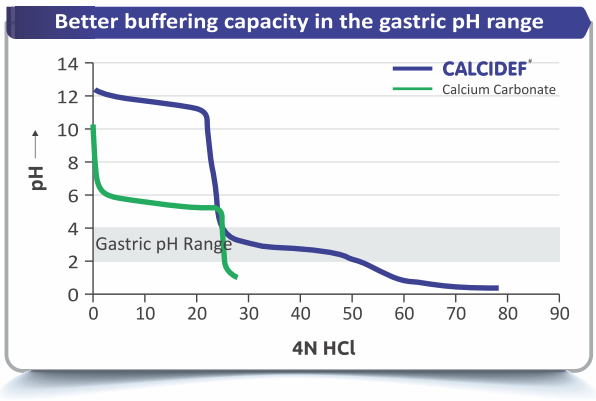

Figure 7. Comparison of buffering capacity of dicalcium malate and calcium carbonate.

From this in vitro tests, it could be concluded that dicalcium malate would not have the gastric problems seen with calcium carbonate. The data may also indicate that there are release rates for each of the calcium atoms.

IN VITRO DISSOLUTION STUDY DATA

An in- vitro comparison of percentage dissolution of Calcidef (Dicalcium malate 400 mg) tablets with calcium carbonate 500 mg, was performed by changeover from acid stage dissolution to various buffers. (Table 3)

The results of in vitro study clearly demonstrated that, when changeover in dissolution was done from acid stage to pH 4.5 stage acetate buffer (fed condition) or changeover in vitro dissolution from acid stage to pH 5.5 citrate buffer (duodenal condition), dicalcium malate remained in solubilized state while in case of calcium carbonate, the quantum of dissolved calcium was approximately 50% in comparison to dicalcium malate.

Table 3. In-vitro comparison of percentage dissolution in various media.

COMPARATIVE DISSOLUTION % (AT 75 RPM, USP APP 2 (PADDLE), 45 MIN TIME POINT AT END STAGE.

Media	Dicalcium malate 400 mg	Calcium carbonate 500 mg
500 ml of 0.1 N HCl (gastric pH)	100.0	55.5
500 ml of 0.1N HCl, followed by 400 ml pH 4.5 Acetate Buffer	97.7	51.7
500 ml of pH 4.5 Acetate Buffer (pH under fed condition)	62.6	4.0
500 ml of Purified water	79.3	2.0
500 ml of pH 5.5 Citrate buffer (duodenal pH)	77.7	9.0
500 ml of 0.1N HCl, followed by 400 ml pH 5.5 citrate buffer	99.2	56.5

Important advantages seen with dicalcium malate over Calcium Carbonate and other Calcium supplements include.

1. Dicalcium malate is soluble across broad range of gastrointestinal milieu pHs and hence gastric acid presence is not essential for dissolution and absorption of calcium from Calcidef. Calcium carbonate containing supplements essentially are required to be taken on empty stomach or presence of acid in stomach is essential to their dissolution and absorption.

2. Patients who are on antacid therapy or therapy with PPIs are also not at risk for calcium absorption from Calcidef since calcium present in Calcidef can get dissolved at higher GI pH values also.

3. It can be taken with or without food owing to its ability to dissolve over entire GI physiological range.

BIOAVAILABILITY STUDIES

The clinical trials have been conducted to assess the bioavailability of dicalcium malate in comparison to calcium carbonate. (Figure 8)

In trial one, a high dose of elemental Ca, 900 mg, was evaluated. In trial two, a moderate dose of elemental Ca, 300 mg, was evaluated.

Methods: Double blind, randomized studies. In both the studies healthy volunteers were given one dose of each product, with a minimum of 1 week washout between supplements, under similar dietary conditions. Blood was taken immediately before supplement administration and at 0.5, 2, 4, 6, 9 and 12 hours after the dose.

Evaluation parameters: The pharmacokinetic measures were the determination of calcium at each time point, as well as area under the concentration-time curve (AUC0-12h), half-life, time at maximum concentration (Tmax) and maximum plasma concentration (Cmax) for calcium.

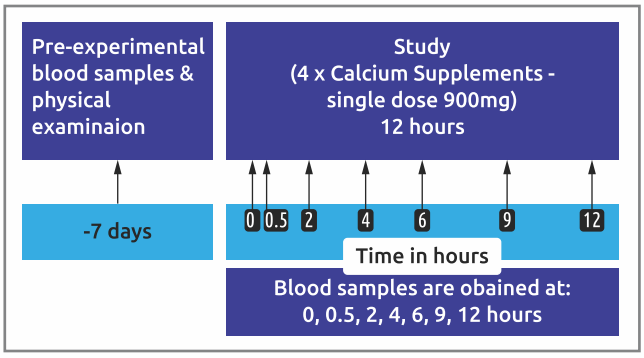

Figure 8: Schematic representation of protocol for the bioavailability studies

Figure below show the differences from baseline values of the dicalcium malate and calcium carbonate serum measurements.

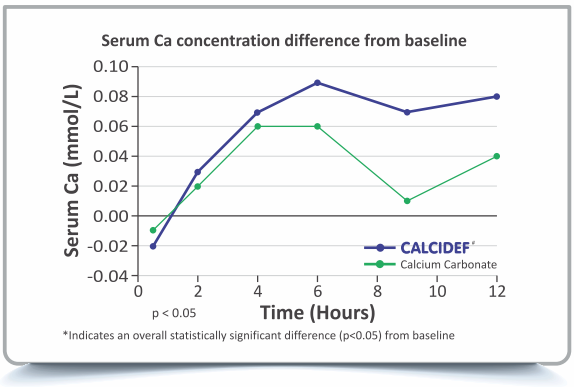

Figure 9: Comparison of serum calcium concentration difference from baseline with dicalcium malate and calcium carbonate trial 1.

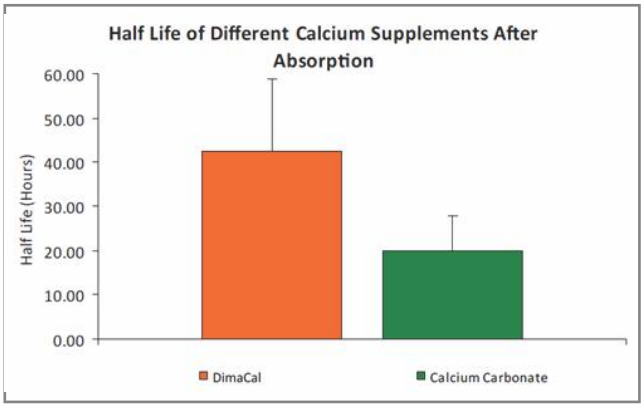

Figure 10 : Half Life of Different Calcium Supplements After Absorption

TRIAL 2: 300MG CALCIUM STUDY:

Results: In the moderate dose study, the dicalcium malate At the 300 mg dose of calcium, Dicalcium malate was again absorbed at a better rate than the calcium carbonate form. The salient data from the 300 mg calcium dose study is depicted in (Figure 11)

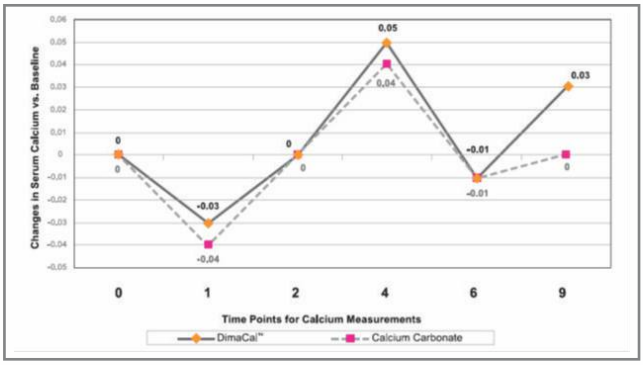

Figure 11. Comparison of serum calcium concentration difference from baseline with dicalcium malate and calcium carbonate trial 2.

CONCLUSION:

1. Dicalcium malate is a unique, patented form of calcium, which contains 2 moles of calcium bound to one mole of malic acid.

2. The compound has a high calcium content, high bioavailability, and is safe and effective.

3. Dicalcium malate appears to be a high calcium containing ingredient that is better absorbed and potentially better tolerated than calcium carbonate.

TOLERABILITY DATA NO ACID REBOUND OR GAS CAUSING PROBLEMS:

One of the problems that can be encountered with calcium carbonate and some of the other alkali calcium forms is the phenomenon of acid rebound and gas after a larger dose of this substance.

To compare dicalcium malate to calcium carbonate for this tendency, an in vitro test was performed. Equal elemental amounts of calcium from dicalcium malate and calcium carbonate were put into separate breakers and then equal amounts of simulated stomach acid was added to each beakers. Calcium carbonate foamed up forming gas bubbles. Calcium carbonate reacts with acidic solutions to produce carbon dioxide gas. While the dicalcium malate did not produce this gas (Figure 12).

From this in vitro test, it appeared that dicalcium malate would not have the gastric problems seen with calcium carbonate. Dicalcium malate contains malic acid which is a natural buffering agent, there is no CO2 production with malic acid thus it is expected that it does not lead to gastric problems.

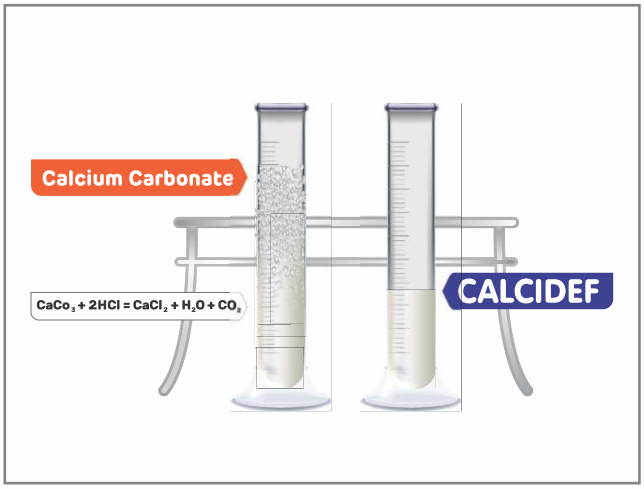

Figure 12. Tendency for gas production with dicalcium malate and calcium carbonate.

SUMMARY OF THE STUDIES

From the above studies, it shows that dicalcium malate is:

1. Superior Absorption Characteristics:

- Absorbed over a longer period of time, resulting in improved calcium blood levels.

2. Does not exhibit the gas causing problems:

- In vitro testing demonstrated dicalcium malate is superior to calcium carbonate.

VITAMIN D

Vitamin D is responsible for enhancing intestinal absorption of calcium and phosphate and therefore plays a key role in the development and maintenance of a healthy skeleton throughout life.

The Institute of Medicine (IOM), USA guidelines suggest a vitamin D sufficient level of 20 ng/ml to optimize bone health. This is in contrast to US Endocrine Society which recommends levels of 30 ng/ml should be attained for children and adults to optimize the probability of good health and avoid other risk associated with vitamin D deficient status. **Thus a recommended dietary allowance (RDA) of 600-800 IU is recommended to maintain adequate levels of vitamin D. In our country, Indian Council of Medical Research (ICMR) recommends a daily supplement of 400 IU/day of vitamin D for Indians under situations of minimal exposure to sunlight.**[30]

ROLE IN CALCIUM ABSORPTION

Calcium absorption occurs by an active saturable system and also by a passive diffusional transport system. 1,25(OH)2D stimulates and mediates active transcellular calcium absorption.[31] **The principal function of vitamin D in calcium homeostasis is to increase calcium absorption from the intestine.**[32] Vitamin D acts in this system by both genomic and nongenomic mechanisms. These mechanisms involve, among other effects, synthesis of a calcium transport protein (calbindin), which shuttles calcium from the brush border across to the basolateral side of the mucosal cell. [33]

Vitamin D in its active form also has the capacity to modify cellular activity, cell differentiation, cell proliferation and therefore may have many roles in physiology and health. Vitamin D receptors have been reported in all tissues including: immune system, brain, heart, pancreas, and intestine, suggesting a role in these tissues. This may explain its association in a wide variety of conditions such as type 1 and type 2 diabetes, multiple sclerosis, schizophrenia, and some cancers.[34] An overview of vitamin D metabolism and its physiological action is presented in (Figure 13)

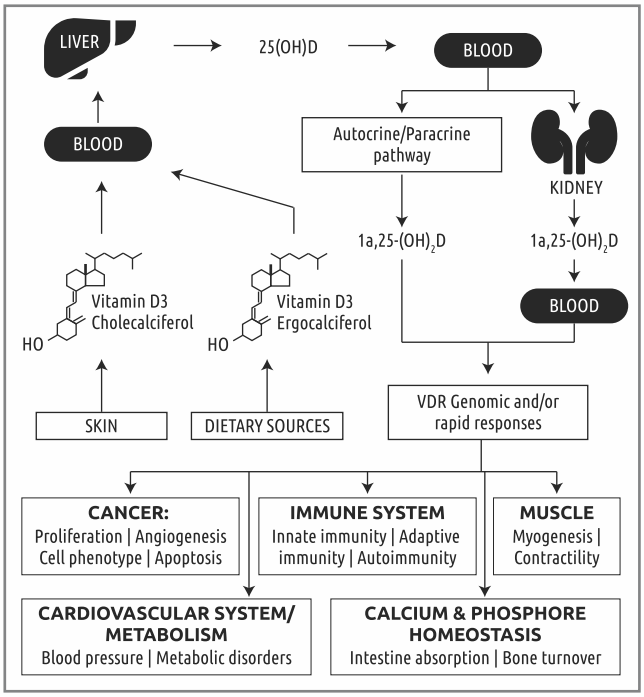

Figure 13. Schematic of vitamin D metabolism and physiological actions.[35]

Calcidef contains vitamin D2 (ergocalciferol) in microencapsulated form and is manufactured with food grade ingredients using spray drying technology to protect sensitive Vitamin D2. After the absorption of ergocalciferol (vitamin D2) from gastrointestinal tract, it is metabolized first to 25 hydroxyvitamin D (25OHD)- Calcidiol, then to the hormonal form 1,25-dihydroxyvitamin D (1,25(OH)2D) - Calcitriol.[36] Calcitriol can be considered as active form of vitamin D, which helps in active transcellular absorption of Calcium. There is also increasing evidence that 1,25(OH)2D3 can enhance paracellular calcium diffusion.[32] Vitamin D appears to have direct and indirect effects on bone development and remodeling, important clinically to prevent rickets in the developing skeleton and osteoporosis and fractures in the aging skeleton. **All ingredients are GMO and allergen free. It is suitable for vegetarians.**

VITAMIN D AND CALCIUM COMBINATION

Appropriate intake of vitamin D and calcium are essential to overall health. Vitamin D helps to maintain adequate serum calcium concentrations to enable normal mineralization of the bone. Vitamin D is needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Thus, calcium and vitamin D work together synergistically on the bone. **The supplementation of calcium along with vitamin D, may improve the absorption of calcium.**[37]

Vitamin D deficiency is also rampant in our country in spite abundance of vitamin D in nature. The prevalence of vitamin D deficiency in India from various Community-based Indian studies ranges from 50% to 94% and from hospital-based studies ranges from 37% to 99%.[38] The individuals who are vitamin D deficient are also at risk of developing calcium deficiency.

Combining vitamin D and calcium into one supplement may increase patient adherence, which in turn improves overall efficacy.[39]

Although the associations between calcium and vitamin D supplementation and bone mineral density, fracture prevention, and potential adverse outcomes from available evidence are inconsistent, the Institute of Medicine Committee and the American Geriatrics Society support a key role of calcium and vitamin D in skeletal health. **Most trials and meta-analysis of vitamin D with or without calcium supplement showed statistically significant reduction in fractures.**[40] A recent systematic review of 26 randomized controlled trials found that calcium supplements, with or without vitamin D, modestly but significantly reduced the risk of total and vertebral fractures, but not fractures of the hip or forearm.[8]

GLYCINE

Glycine is the smallest non-essential, non-polar, non-optical, glucogenic and metabolically inert amino acid, with a carbon atom bound to two hydrogen atoms, and to an amino and a carboxyl group. Chemical structure is depicted in Figure 14.

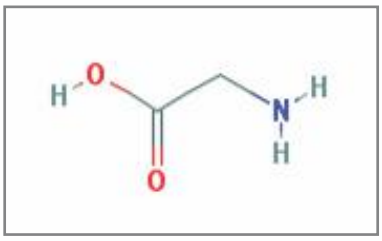

Figure 14. Chemical structure of glycine.

This amino acid is an essential substrate for the synthesis of several biologically important biomolecules and compounds. Glycine acts as precursor for several key metabolites of low molecular weight such as creatine, glutathione, haem, purines, and porphyrins. Glycine is very effective in improving the health and supports the growth and well-being of humans and animals.[41] Dietary supplementation of proper dose of glycine is effectual in treating metabolic disorders in patients with cardiovascular diseases, several inflammatory diseases, obesity, cancers, and diabetes. Glycine also has the property to enhance the quality of sleep and neurological functions. Glycine helps to trigger the release of oxygen to the energy requiring cell-making process and is important in the manufacturing of hormones responsible for a strong immune system.

GLYCINE IN BONE HEALTH

The organic matrix is comprised predominantly of type I collagen (90–95%) with contributions from various other proteins. The triple-helical structure of collagen arises from an unusual abundance of three amino acids: glycine, proline, and hydroxyproline (Figure 15). Every 3rd amino acid there is a glycine moiety. Each amino acid has a precise function.[42] Glycine, which is 33% of collagen residues, play a special role in collagen structure and its insufficient availability could be a cause to make collagen synthesis and regeneration difficult. Glycine, the most necessary amino acid for collagen synthesis, thus it must be incorporated into the diet as a nutritional supplement.[43]

Multiple collagen fibrils form into collagen fibres. Amino acids on the alpha chain proline (PRO), glycine (GLY) and hydroxyproline (HYP).[44]

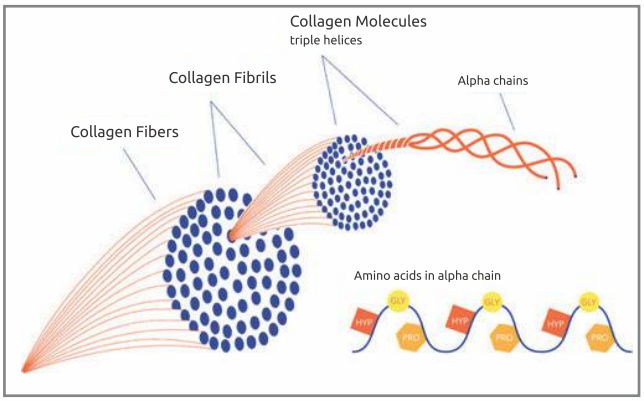

Figure 15. Structure of collagen fiber.

FOLIC ACID[45]

Folic acid also called vitamin B-9, is a water-soluble B-complex vitamin. Folic acid is the synthetic form of folate, which is a naturally occurring B vitamin. Folate helps make DNA and other genetic material.

Folate has multiple functions in the body which include, production of new red blood cells. Without enough folate, a person can also develop a type of anemia called folate deficiency anemia .Folate is also important for the synthesis and repair of DNA and other genetic material, and it is necessary for cells to divide. Folate is found naturally in foods such as leafy green vegetables, oranges, and beans. Reduced forms of folic acid are required for essential biochemical reactions that provide precursors for the synthesis of amino acids, purines, and DNA.

It is particularly important to get enough folate during pregnancy. Folate deficiency during pregnancy can lead to neural tube irregularities, such as spina bifida and anencephaly.

Some symptoms of folate deficiency include: weakness, fatigue, trouble concentrating, headache, irritability, heart palpitations, sores on the tongue and inside the mouth, a change in color of the skin, hair, or fingernails and shortness of breath

Folate deficiency is relatively common, even though the deficiency is easily corrected by administration of folic acid. Women are especially susceptible to folate deficiency during pregnancy, which is a period of rapid fetal growth, and high rates of cell division.[46]

Other groups at increased risk of folate deficiency include:

- people with alcohol use disorder
- people of childbearing age
- people with conditions that affect nutrient absorption, including IBD and celiac disease
- people with MTHFR polymorphism

As per the joint SOGC-MOTHERISK Clinical Practice guidelines, folic acid in combination with multivitamin has been shown to reduce birth defects-NTD, heart defects, urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis.[47]

COMPOSITION OF CALCIDEF

		% RDA
Dicalcium Malate 1379.3mg equivalent toelemental calcium	400 mg	66.67
Vitamin D2	400 IU	---
Folic Acid	100 mcg	100
Glycine	10 mg	---

Figure 16. Composition of Calcidef.

DOSAGE

Recommended Usage: One tablet daily for adults. Not to exceed the stated recommended daily usage.

INDICATION

As health supplement, for human well-being.

SUMMARY

Adequate calcium intake is essential for the maintenance of bone health during growing phases and the preservation of bone mineral density in elderly individuals. Due to multiple reasons, many individuals do not secure adequate nutrients from diet alone. Supplementation with various calcium supplements is the most widely used approach to increase calcium intake.

There are several calcium salts and formulations available in the market. Albion has developed a new, patented form of calcium—Dicalcium Malate. As the name suggests, it is comprised of 2 moles of calcium attached to one mole of malic acid.

Dicalcium Malate was developed to give manufacturers of dietary supplements a better alternative to calcium carbonate and other salt forms. Dicalcium Malate has 29% elemental calcium. For calcium supplements to be clinically useful, they must have optimal bioavailability.[26] A study which compared Dicalcium malate and calcium carbonate showed that, Dicalcium malate was significantly better absorbed than calcium carbonate and it maintained an elevation in serum calcium for a much longer period of time, indicating a greater half-life, this could be a reflection of the higher presence of the calcium in an absorbable form for a longer time period which could be related to the chemistry of this patented mineral form.

SALIENT FEATURES

Calcidef is a combination Dicalcium malate, Vitamin D2, folic acid and glycine with below advantages:

- **Dicalcium maleate**
  - o Elemental calcium of 29%
  - o Patented Calcium with Superior absorption
  - o 2 moles of calcium: - *Sequential absorption: Absorbed over a longer period of time, resulting in improved calcium blood levels*
  - o Higher half-life as compared to calcium carbonate
  - o Soluble across broad range of GI pH
  - o Can be taken with or without food owing to its ability to dissolve over entire GI physiological range
  - o Patients taking PPIs can also take

- Related higher calcium content as compared to calcium citrate malate

- Malic acid:
Better solubility

- Natural buffering agent: Does Not exhibit the gas causing problems unlike calcium carbonate

- **Water soluble Vitamin D2:**
  - Rapid absorption
  - Higher bioavailability
  - Improved stability compared to oil based formulations
- **Glycine**
  - Known to be component of collagen fibers

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NOTES

CALCIDEF™

Dicalcium Malate 400mg, Vit D2 400 IU, Folic Acid 100mcg, Glycine 10mg Tablets

Calcium with a **DIFFERENCE**

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