Calcium citrate: role, function and clinical applications

Filomena Cetani, Anna Dal Lago, Laura Pierotti, Simone Della Valentina, Chiara Sardella, Elena Pardi

Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

ABSTRACT

Adequate calcium intake is crucial for bone health and overall bodily functions. However, modern diets often lack sufficient calcium, making supplementation necessary, especially in the presence of certain health conditions. The most common calcium supplements include calcium carbonate and calcium citrate.

This review focuses on the latter, exploring its mechanisms, clinical uses, and therapeutic applications. Calcium citrate is preferred in certain situations, including:

- chronic hypoparathyroidism: ideal for individuals intolerant to calcium carbonate or those using proton pump inhibitors, calcium citrate does not depend on stomach acid for absorption;
- osteoporosis: by supporting bone density, calcium citrate helps strengthen bones and reduce fracture risk in individuals with osteoporosis;
- hypochlorhydria: being better absorbed than other forms of calcium, calcium citrate is beneficial for individuals with hypochlorhydria (low gastric acid production);
- bariatric surgery: this surgery affects nutrient absorption, and calcium citrate ensures adequate calcium intake in patients with impaired absorption.

In conclusion, calcium citrate is widely used in clinical practice for various medical conditions requiring calcium supplementation.

KEYWORDS

Calcium, calcium supplements, chronic hypoparathyroidism, bariatric surgery, hypochlorhydria, osteoporosis.

Calcium: intake and role

Daily calcium needs should primarily be met through dietary intake. According to the International Osteoporosis Foundation, recommended calcium intake varies depending on sex, age, and certain conditions. The recommended daily intake for both women and men aged 19 to 50 years is 1000 mg. This increases to 1200 mg from the age of 51 in women, and after 70 in men [1].

Approximately 20-30% of ingested dietary calcium is absorbed by the gut. Intestinal calcium absorption occurs through two mechanisms: the transcellular and the paracellular pathways. Transcellular absorption is an active, energy-dependent process that takes place in the duodenum. It is dependent on the concentration of calcium-binding proteins and is rapidly saturable. It requires active vitamin D and is responsible for most of the calcium absorption that occurs in individuals with low to normal calcium intake. The paracellular mechanism, on the other hand, is passive and does not require energy. It occurs throughout the intestine and, being independent of calcium concentration in the gut lumen, is not rapidly saturable. This process is not vitamin D dependent and accounts for most of the calcium absorption in individuals with high calcium intake [2,3] (Table I).

The skeleton is the body's primary calcium reservoir, containing approximately 99% of its total calcium (Fig. 1), which is organized into hydroxyapatite complexes that confer strength and structure on bone. The remaining approximately 1%, referred to as "non-bone calcium," is present in the bloodstream in different forms: as free ions, bound to albumin and other proteins, or complexed with other ions (Figure 1). This "non-bone calcium" plays a crucial role in physiological functions such as muscle contraction and nerve impulse transmission [4,5]. Consequently, its concentration in bodily fluids is meticulously regulated by calciotropic hormones [6].

Article history
Received 21 Feb 2025 – Accepted 31 Mar 2025

Contact
Filomena Cetani; filomena.cetani@unipi.it
Department of Clinical and Experimental Medicine University of Pisa, Pisa, Italy
Phone: +39 050 995040

Calcium supplements

When a diet rich in dairy products and calcium-fortified water is insufficient, calcium supplements can be utilized. The most common are calcium carbonate and calcium citrate [7]. The proportion of elemental calcium in calcium citrate is 20%, versus 40% in calcium carbonate. Absorption of these supplements occurs via paracellular transport and is influenced by their solubility, which varies with pH. Specifically, solubility decreases as pH increases. The solubility of calcium carbonate is highly dependent on an acidic pH, necessitating its intake

Int J Bone Frag. 2025; 5(1):2-5
https:doi.org/10.57582/IJBF.250501.002

after meals. Conversely, calcium citrate can be taken after or between meals as it remains soluble at higher pH values [7-9]. A meta-analysis by Sakhaee *et al*. demonstrated that calcium citrate is better absorbed than calcium carbonate, whether taken on an empty stomach or with meals [10]. Additionally, calcium citrate is associated with fewer gastrointestinal disorders and a lower incidence of kidney stones compared with calcium carbonate [7-9] (Table II).

Citrate

As its name implies, another component of calcium citrate is citrate itself. Citrate accounts for 5% of the organic component of bone tissue and makes up 1-2% of total bone tissue. Approximately 90% of citrate is deposited in bone tissue, which serves as its storage reservoir, with only a small fraction circulating in the bloodstream.

In urine and in soft tissues, citrate binds with calcium ions to prevent the precipitation of calcium salts and thus the formation of harmful deposits. In routine practice, citrate is considered both a diagnostic and a therapeutic tool: it is measured in urine to assess the risk of kidney stones and is also administered, in the form of potassium and magnesium salts, to patients with kidney stones to prevent recurrences [9,11,12].

In the skeleton, citrate undergoes continuous turnover; it is removed during bone resorption and deposited between the apatite crystals during the bone formation process. It has been demonstrated that urinary citrate excretion may be associated with low bone mass[9]. .In contrast, other authors have reported a positive correlation between urinary citrate excretion and bone mineral density at various skeletal sites [11,12].

Calcium citrate: function and clinical applications

The clinical applications of calcium citrate include its therapeutic use in hypoparathyroidism, bone fragility, bariatric surgery, and achlorhydria.

Table I Summary of the key differences, in terms of function, regulation, and role in calcium absorption, between the paracellular and transcellular mechanisms.

CHARACTERISTIC	PARACELLULAR ABSORPTION	TRANSCELLULAR ABSORPTION
Mechanism	Passive, energy-independent	Active, energy-dependent
Site of action	Throughout the intestine	In the duodenum
Vitamin D dependence	Independent of vitamin D	Dependent on vitamin D
Calcium concentration dependence	Independent of calcium concentration in the gut lumen	Dependent on the concentration of calcium-binding proteins
Saturability	Not rapidly saturable	Rapidly saturable
Role in calcium absorption	Promotes high calcium absorption	Promotes low to normal calcium absorption

Figure 1 Calcium localization and function.

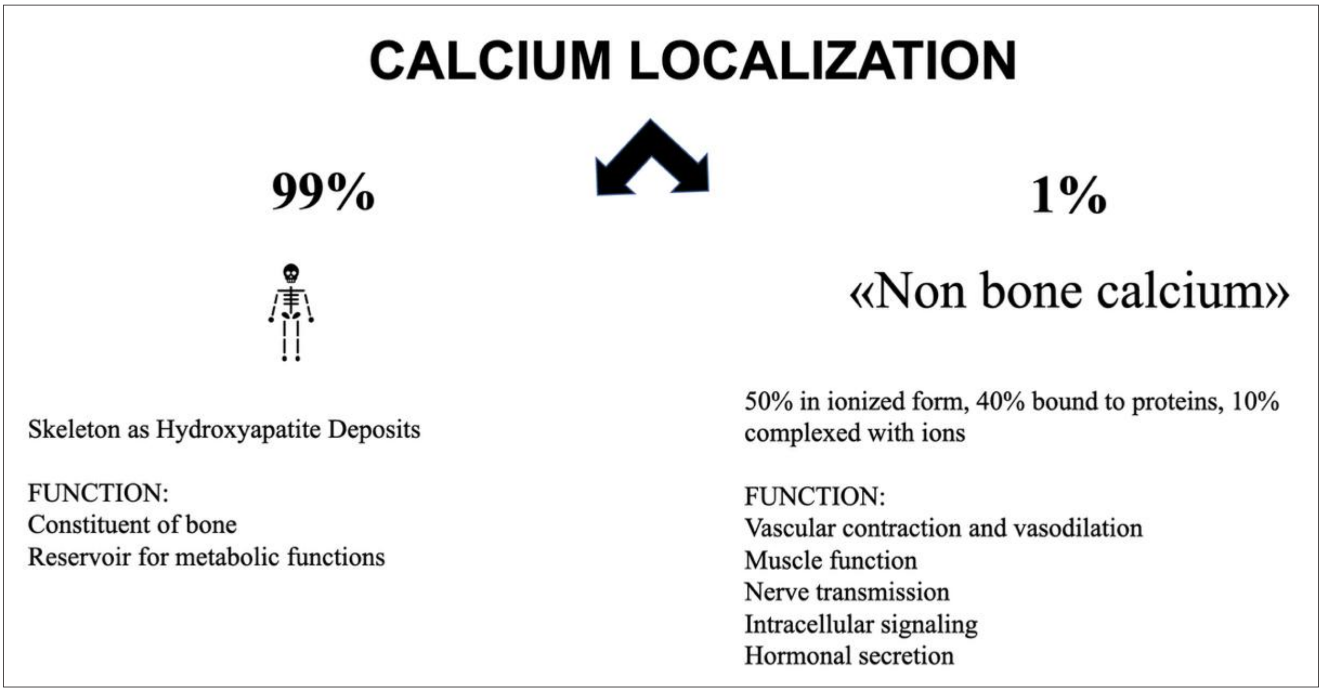

Table II Summary of the key differences between calcium citrate and calcium carbonate, in terms of elemental calcium content, absorption characteristics, gastrointestinal tolerance, and other important clinical factors.

CHARACTERISTIC	CALCIUM CITRATE	CALCIUM CARBONATE
Elemental calcium content	Contains 20% elemental calcium	Contains 40% elemental calcium
Absorption mechanism	Absorption occurs via paracellular transport	Absorption occurs via paracellular transport
Solubility and pH dependence	Soluble at higher pH values, allowing for intake between meals	Solubility highly dependent on acidic pH, necessitating intake after meals
Gastrointestinal tolerance	Associated with fewer gastrointestinal disorders	May cause more gastrointestinal issues, such as bloating and constipation
Kidney stones	Lower incidence of kidney stones compared with calcium carbonate	Higher risk of kidney stones due to higher calcium load and solubility issues
Recommended intake timing	Can be taken with or without food, flexible intake schedule	Recommended to be taken with meals to enhance absorption

Hypoparathyroidism

Currently, calcium supplements are the cornerstone therapy for hypoparathyroidism. Calcium carbonate is the most widely used supplement, but calcium citrate is preferred for patients with gastrointestinal disorders. Additionally, the presence of citrate may help prevent nephrolithiasis [9,13,14]. In a double-blind, crossover trial, Naciu *et al*. evaluated 24 adults with postsurgical chronic hypoparathyroidism treated with calcium citrate or calcium carbonate. No statistically significant difference was found between the treatment groups, except for a significantly lower oxalate/creatinine ratio in the patients receiving calcium citrate. This finding might be related to the reduced risk of kidney stone formation observed in the calcium citrate group, considering that oxalate is one of the main promotors of stone formation [14].

Bone fragility

Calcium carbonate is the most used supplement in clinical studies evaluating bone fragility [8,15]. However, several studies have shown that calcium citrate has increased solubility and, compared with calcium carbonate, depends less on estrogen and vitamin D treatment in order to be absorbed. This is clinically significant, as many women do not take estrogen and have low levels of vitamin [9,15-18].

Achlorhydria

Calcium citrate is soluble at higher pH values, meaning that it may potentially be suitable for achlorhydric subjects and patients using proton pump inhibitors (PPIs). However, there is no scientific evidence to support this. D. Additionally, given that achlorhydria increases with age and osteoporotic patients are often elderly, the use of calcium citrate is advisable [9,16].

Bariatric surgery

The most common bariatric surgical procedures today are Roux-en-Y gastric bypass and sleeve gastrectomy. The former causes calcium malabsorption due to the exclusion of the duodenum and proximal jejunum, which are the sites of transcellular calcium transport. Additionally, patients often develop a vitamin D deficiency. Furthermore, the surgical intervention and frequent use of PPIs can lead to achlorhydria. Instead, the impact of sleeve gastrectomy on calcium absorption is debated. The anatomy of the absorption sites is not altered, and so absorption should not be affected. However, vitamin D deficiency and the use of PPIs, which can affect calcium absorption, are both common in these patients. Several guidelines on bariatric surgery recommend calcium supplements for all patients [9,19-22].

Conclusions

Calcium citrate is a versatile and widely applicable supplement in clinical practice, particularly for individuals with specific absorption challenges or conditions affecting calcium metabolism.

References

1. International Osteoporosis foundation (IOF), 2025. Calcium recommendations. Available at: https://www.osteoporosis.foundation/educational-hub/topic/calcium/calcium-recommendations. Accessed March 10, 2025.
2. Shkembi B, Huppertz T. Calcium absorption from food products: food matrix effects. Nutrients. 2022;14(1):180.
3. Fleet JC. Vitamin D-mediated regulation of intestinal calcium absorption. Nutrients. 2022;14(16):3351.
4. Matikainen N, Pekkarinen T, Ryhänen EM, Schalin-Jäntti C. Physiology of calcium homeostasis: an overview. Endocrinol Metab Clin North Am. 2021;50(4):575-90.
5. Yu E, Sharma S. Physiology, calcium. 2023 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
6. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5 Suppl 1:S23-30.
7. van der Velde RY, Brouwers JR, Geusens PP, Lems WF, van den Bergh JP. Calcium and vitamin D supplementation: state of the art for daily practice. Food Nutr Res. 2014;58.
8. Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract. 2007;22(3):286-96.
9. Palermo A, Naciu AM, Tabacco G, et al. Calcium citrate: from biochemistry and physiology to clinical applications. Rev Endocr Metab Disord. 2019;20(3):353-64.
10. Sakhaee K, Bhuket T, Adams-Huet B, Rao DS. Meta-analysis of calcium bioavailability: a comparison of calcium citrate with calcium carbonate. Am J Ther. 1999;6(6):313-21.
11. Vezzoli G, Magni G, Avino M, Arcidiacono T. Ruolo del citrato nel metabolismo osseo. G Clin Nefrol Dial 2020;32:15-20.

12. Caudarella R, Vescini F, Buffa A, Stefoni S. Citrate and mineral metabolism: kidney stones and bone disease. Front Biosci. 2003;8:s1084-106.
13. Rosa M, Usai P, Miano R, et al.; International Translational Research in Uro-Sciences Team (ITRUST). Recent finding and new technologies in nephrolithiasis: a review of the recent literature. BMC Urol. 2013;13:10.
14. Naciu AM, Tabacco G, Bilezikian JP, et al. Calcium citrate versus calcium carbonate in the management of chronic hypoparathyroidism: a randomized, double-blind, crossover clinical trial. J Bone Miner Res. 2022;37(7):1251-9.
15. Kenny AM, Prestwood KM, Biskup B, et al. Comparison of the effects of calcium loading with calcium citrate or calcium carbonate on bone turnover in postmenopausal women. Osteoporos Int. 2004;15(4):290-4.
16. Recker RR. Calcium absorption and achlorhydria. N Engl J Med. 1985;313(2):70-3.
17. Heller HJ, Poindexter JR, Adams-Huet B. Effect of estrogen treatment and vitamin D status on differing bioavailabilities of calcium carbonate and calcium citrate. J Clin Pharmacol. 2002;42(11):1251-6.
18. Thomas SD, Need AG, Tucker G, Slobodian P, O'Loughlin PD, Nordin BE. Suppression of parathyroid hormone and bone resorption by calcium carbonate and calcium citrate in postmenopausal women. Calcif Tissue Int. 2008;83(2):81-4
19. Sakhaee K. Bariatric surgery and effects on calcium and bone metabolism. Clin Rev Bone Miner Metab. 2014;12(4):240-51
20. Tondapu P, Provost D, Adams-Huet B, Sims T, Chang C, Sakhaee K. Comparison of the absorption of calcium carbonate and calcium citrate after Roux-en-Y gastric bypass. Obes Surg. 2009;19(9):1256-61.
21. Sakhaee K, Griffith C, Pak CY. Biochemical control of bone loss and stone-forming propensity by potassium-calcium citrate after bariatric surgery. Surg Obes Relat Dis. 2012;8(1):67-72.
22. Via MA, Mechanick JI. Nutritional and micronutrient care of bariatric surgery patients: current evidence update. Curr Obes Rep. 2017;6(3):286-96.

Acknowledgments: *None.*
Conflicts of Interest Statement: *The authors declare that there is no conflict of interest.*