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The importance of the type of preparation of calcium and vitamin D in the prevention and treatment of osteoporosis

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Summary
Most Europeans do not meet the adequate intake for calcium and vitamin D; supplementation of both can help to meet requirements. Inappropriate intake can lead to reduced calcium absorption, higher bone remodeling rates and increased bone mass loss. Also, vitamin D deficit has been linked to reduced muscle function and increased risk of falling. Calcium from carbonate is the most common form, due to its cost-effectiveness profile, of calcium supplement for choice. Calcium lactate and gluconate are less concentrated forms of calcium and are not practical oral supplements. The purpose of the present article is to examine the importance of the combination calcium-vitamin D its role in the prevention and management of osteoporosis and the most common and useful formulations for its clinical use.

Key words: *Calcium supplements, Vitamin D, Osteoporosis, Postmenopause.*

1. Introduction

The prevention of osteoporosis continues to be one of the areas of unfinished business in public health and which will become more relevant as the population ages. This disorder is characterised by a greater bone fragility and an increase in the risk of having fractures, located most frequently in the spine and hip, although any bone may become affected[1]. In our country, the annual incidence of hip fractures for this reason is 400 cases per 100,000 women over 50 years of age. The vertebral fracture is the osteoporotic fracture with a higher incidence in women and in males. Its annual incidence is 1,250 cases per 100,000 women and has been demonstrated to be a significant risk factor for other osteoporotic fractures and even for mortality[2].

Calcium and vitamin D are nutrients of great importance and absolutely essential for the acquisition and maintenance of bone health. The supply of calcium and vitamin D is critical throughout life; first to achieve a bone mass which is both quantitatively and qualitatively adequate and, subsequently, when from the age of 30 it begins to diminish. Unfortunately, at least within the population of the theoretically developed countries, 85-90% of the female population doe not ingest sufficient calcium and more than 50% of postmenopausal osteoporotic women have inadequate levels of vitamin D[3,4].

At the margins of its relevance in bone metabolism, calcium is essential for neuromuscular activity, coagulation of blood and adequate cardiac function. As has already been indicated, it is a vital component of bone architecture and necessary for the correct deposition of minerals throughout life. More than 99% of calcium present in the organism is found in the bones and teeth, exercising the function of reservoir. When the dietary supply is not sufficient for the maintenance of the levels of extracellular liquid (ECL) and plasma necessary for the maintenance of the vital functions in which it participates, mechanisms for obtaining calcium from the bone reservoir are activated, by which negative balance is produced in the bone. Calcium is absorbed in the small intestine with the help of vitamin D. It is eliminated through renal excretion, although a small proportion is found in the faeces. The kidney does not only participate in the excretion, but in the joint management of calcium, increasing the excretion or the re-absorption as is appropriate to the body's homeostasis of calcium.

2. Calcium

2.1.Calcium deficit in nutrition

The needs of calcium for an adult are reflected in the daily supply necessary for the maintenance of calcium homeostasis and the integrity of the skeleton. The amount necessary for a European adult is 800 mg daily[5]. After the menopause, the requirements increase up to at least 1,000 mg/day[6,7], although the WHO quantify their recommendation for European women at 1,300 mg/day[8,9].

Those people who do not obtain a sufficient intake of dietary calcium should supplement this, with the aim of reaching the daily minimum requirements. The evidence suggests that the average citizen does not even reach the low end of the daily recommended consumption. Women who are in their forties report a calcium intake of 50% of that recommended for postmenopausal women 10. In a study carried out in nine European countries to confirm the dietary requirements of European postmenopausal and osteoporotic women, the results indicate that only 37.2% of the population studied were found to be in treatment with calcium supplements (64.2% of the Spanish population). However, only 19.1% of those surveyed reached the daily intake of 1,300 mg/day recommended by the WHO (in our country, 50% of patients in treatment with supplements receive between 800 and 1,300 mg and 28%, doses higher than 1,300 mg/day). Among the population aged over 75 years, only 17.1% reached the recommended requirements, while among those younger than 75 years that figure was 20.5%[4].

2.2. Calcium supplements

With the aim of assuring a correct intake of calcium, there is a range of supplements currently on sale in our country (Table 1). The most commonly used, and best studied, are the carbonate and citrate forms, although the latter is not available in our environment; but it is true that some preparations contain citric acid as an excipient which may facilitate the transformation of carbonate into citrate. The bioavailability of the calcium ion is 20-30%, being absorbed in the duodenum and jejunum, by means of a mechanism of passive diffusion. The mechanism for the absorption of calcium is a saturable process, which means that at a dose of around 500 mg, absorption diminishes intensely. The absorption has a variable efficiency since it depends on a multitude of factors, among others: diet, age, rate of growth, vitamin D contained in the diet and the requirements for calcium. Foods rich in glucose, lactose or galactose increase notably the bioavailability of calcium. The absorption of a specific salt of calcium depends on the one hand on its capacity for disassociation, different for the various salts and slightly favouring the citrate and pidolate forms, and on the other, its capacity for dissolution. There are marked differences in the dissolution of the preparations of calcium supplements, in principle supposedly due to differences in pharmaceutical formulation, although experience shows that not all preparations of the same salt exhibit equivalent absorption[11-13].

Calcium carbonate possess the highest proportion of calcium element among the different salts[14]. This translates, from the patient's perspective, into the need for a lower daily requirement of tablets to reach the dose to be provided. The way of ensuring an optimum absorption is to take the tablets with meals, dividing the doses higher than 500 mg into a number of smaller amounts. The

Table 1. Formulations of calcium supplements currently marketed in our country

Formulation	Calcium content (%)	Recommended daily dose (mg de Ca)	Interval of administration (h)	Dose contained in a unit (mg de Ca)	Form: in association with vit. D, or not
Carbonate	40	500-1,200	24	500	- Without association - Vitamin D
Phosphate	38.8	1,200	24	1,200	- Without association - Vitamin D
Pidolate	13.5	1,000-1,500	8-12	500	- Without association - Vitamin D
Lactate	12.9	500-1,000	6-12	250	- Vitamin D
Lactogluconate	6.8	1,000	24	500	- Carbonate + Vitamin D
Glubionate	6.5	500-1,500	24	500	- Carbonate

secretion of gastric acid and, definitively, gastric pH, plays a very important role in the intestinal disassociation of the carbonate, with the bioavailability of the carbonate and citrate forms being equivalent in these circumstances[11,15]. However, other studies indicate that the citrate form, even under these circumstances has a higher bioavailability than the carbonate, although authors themselves indicate that these differences may be due to deficiency in the secretion of gastric acid in the individuals participating in the study[16]. This fact acquires relative importance in older patients, with hypo- or achlorhydria, or gastrectomy, in whom the bioavailability of the carbonate form may be found to be diminished. One study, crossed and randomised, shows that the inhibitor of the proton pump, omeprazol, notably reduces the fraction of calcium absorbed from calcium carbonate in postmenopausal women after 12 hours of fasting[17]. In addition, another case-controlled study shows that the long term treatment with proton pump inhibitors, especially when high doses are used, are associated with an increase in the risk of hip fracture[18].

Calcium supplements are generally well tolerated. However, a recent report of the Women's Health Initiative (WHI) from the US reveals the absence of statistically significant differences in the incidence of adverse gastrointestinal effects (gases, abdominal distension, constipation) between patients to whom had been administered a placebo and those administered a calcium/vitamin D combination[19]. In clinical practice, up to 50% of patients report gastrointestinal symptoms - constipation, flatulence and abdominal distension – after the ingestion of these preparations. Usually the carbonate form is associated with a higher frequency of these adverse affects, although it is also recommended that the citrate form be substituted by the carbonate form if the symptoms appear in association with the former[20]. Additionally, in patients who report poor tolerance, it is recommended that the combined calcium/vitamin D be started at a low dose, increasing it later until the required dose is reached after 1-2 months.

Certain studies on the safety of those compounds[19] have generated controversy as to at what point calcium and vitamin D supplements increase the risk of renal lithiasis. Patients randomly chosen to receive 1,000 mg/day of calcium and 400 UI/day of vitamin D_3 had a 17% higher risk of suffering renal lithiasis with respect to the placebo group. However, apparently the women included in the group treated with supplements self-medicated to a significant degree, reaching a daily calcium intake of 2,000 mg. Recent studies suggest that a diet poor in calcium can increase the risk of lithiasis[21]. It is recommended that supplements be taken with food to facilitate the union of calcium with oxalates in the intestine, and not to exceed the maximum recommended dose.

A recently published study has given the supplements a dubious role in being transformed into an independent cardiovascular risk factor, although this assertion is far from being demonstrated[22] and has subsequently been challenged by other authors[23] . In all cases, it should not be forgotten that the total dietary intake of calcium for each patient should be considered before calculating the necessary dose of supplements.

3. Vitamin D

3.1. Physiology

Vitamin D has a significant influence on good bone health. Among its functions can be highlighted: the regulation of the intestinal absorption of calcium and the stimulation of resorption in cases where it is necessary to increase the concentration of blood calcium; it also contributes to the maintenance of normal levels of calcium and phosphorus in the blood. UVB radiation is absorbed by 7-dehydrocholesterol which exists in the skin, to form previtamin D_3. Previtamin D_3, is, on the other hand an unstable compound and it rapidly transforms by the action of heat, into vitamin D_3[24]. Vitamin D_3 reaches the extracellular space and from here, the capillaries, where it combines with the vitamin D transporter protein (DBP)[25]. Once in the capillaries, the vitamin D reaches the liver, where it undergoes hydroxylation which results in the formation of 25-hydroxyvitamin D [25(OH)D]. The 25(OH) once again bonds with the DBP and progresses to the kidney where it is transported to and released in the tubular renal cell and again hydroxylated, forming 1.25-dihydroxyvitamin D[1.25 $(OH)_2$ D][26]. This the biologically active form of vitamin D and that which is responsible for the homeostasis of calcium. The vitamin D contained in foodstuffs reaches the lymphatic system through the chylomicrons, entering the bloodstream and binding themselves to the DBP[26]. From here they will later reach the liver and kidney to be transformed into the active form of vitamin D.

The main natural sources of vitamin D are sunlight and diet (< 10%) which essentially includes: blue fish, such as salmon, mackerel, tuna, bonito, horse mackerel, sardines and other fortified foods such as milk, yoghurts and some cereals[25,27]. Despite a high consumption of blue fish, surveys of dietary habits in Spain show that the intake of vitamin D is notoriously insufficient, 208 ± 4 UI/day, whilst in postmenopausal women it is 168 ± 14 UI/day, when it should be reaching 800-1,000 UI/day[28]; and what is more significant, it is insufficient since infancy. In Calatan and Canarian children the daily intake of vitamin D is 120-96 and 60-75 UI/day, respectively[29].

Blood calcidiol [25 (OH)D] is the best metabolite of vitamin D to be dosed and its blood levels are considered to be a very useful index for the management of optimum levels of vitamin D. It is considered by different authors that the lower limit of normality is 10 to 15 ng/ml, although it is known that levels of PTH increase with values of calcidiol from 25 to 30 ng/ml; from all this it can be concluded that desirable values of calcidiol would be above 40ng/ml[30,31].

Approximately 95% of Spanish people over 70 years of age do not have a sufficient intake of vitamin D from the diet. Fortunately, our benign climate with a generous exposure to sunlight, reduces the deficit to 56% in winter and even down to 28% during the summer months[32].

However, in recent times, the emphasis put on the necessary use of sun protection has counteracted to some extent the potential benefits spelled out by various authors of a sunny country such as ours, and this could be one of the causes of the high prevalence of vitamin D deficit. Currently, the recommendations of the panels of experts are centred on recommending an intake of 1,000-2,000 UI/day to prevent the development of this deficiency[33].

Figure 1 represents the biological activity of vitamin D, responsible for the homeostasis of calcium.

3.2. Calcium-vitamin D interaction

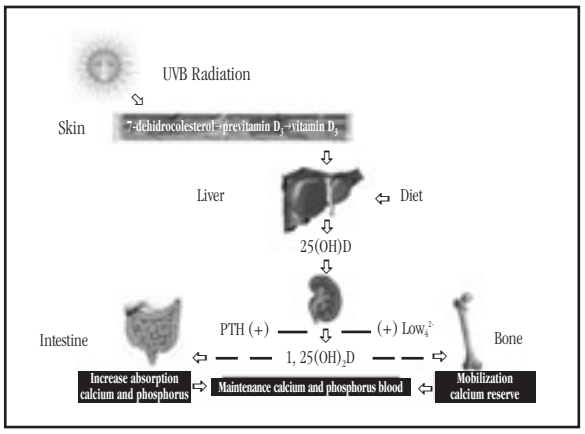
The increase in the administration of vitamin D and of 25-hydroxyvitamin D (25(OH), brings with it a consequent increase in the metabolites 1,25-dihydroxyvitamin D and 24.25-dihydroxyvitaimin D and as a consequence, of the absorption of calcium and of the concentration of calcium ions in circulation[34]. When the levels of parathormone (PTH) are low, the stimulus which facilitates bone resorption ceases, which for a long time was thought to be an essential mechanism by which vitamin D contributes to the improvement in mass and strength of bone. However, it has been observed that on other occasions, it is the increase in the supply of calcium in the diet, that is responsible for the increase in the gastrointestinal absorption of this ion, and of the concentration of circulating calcium ions, while the rates of PTH and biochemical markers for bone turnover diminish. A recent study has contributed to the clarification of the relationship that exists between calcium, PTH and 25(OH)D[35]. According to the results of this study, it seems clear that the suppression of PTH depends more on the levels of blood calcidiol than on the intake of calcium, and therefore, when the levels of blood calcidiol are sufficient (≥ 25 nM) an ingestion of calcium of 800 mg may be sufficient for the maintenance of the homeostasis of calcium. On the other hand, another study corresponding to the same period of time, indicates that the supply of calcium does not have any impact on the relationship between the supply of vitamin D and the blood concentration of 25(OH)D[36].

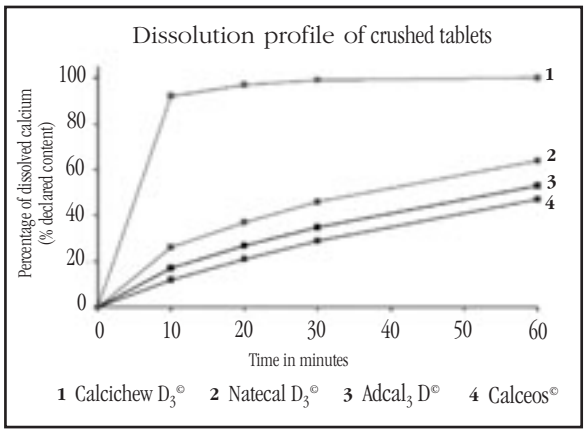
This evidence therefore suggests that the requirements for vitamin D are independent of the external supply of calcium. The levels of vitamin D are related to the bone mass in young adults, and their supplementation diminishes the percentage of loss of bone mass in adults[37].

4. Administration of calcium combined with vitamin D

As has been referred to earlier, the association between calcium carbonate and vitamin D in the great majority of commercial preparations brings with it an increase in the absorption of calcium as a result of the interaction of these two compounds. In fact, a study carried out with the objective of quantifying the absorption promoted by cholecalciferol, found an up to 16.6% higher accumulated secretion of this ion when administered

Figure 1. Biological activity of vitamin D.
Figure 2. Dissolution profile of Mastical D© (Calcichew D_3©) and other reference products (Natecal D©, Adcal D© and Ideos©) once crushed. The composition of the 4 formulations is: vitamin D_3, 400 UI and calcium carbonate, 500 mg per Mastical D© and Ideos© and 600 mg for Natecal D© and Adcal D©).





in combination with vitamin D supplements[38]. However, it has also been mentioned in another chapter of this article, that there may be marked differences in the dissolution of the preparations of calcium supplements, supposedly due to their pharmacological formulation, although not all the preparations of the same salt exhibit the same absorption. Among other factors, the possibility that the combined tablets are chewable gives the USP (United States Pharmacopeia) dissolution test an availability which is perfectly correlatable, *in vitro-in vivo*[39,40]. These results motivated the authors to carry out a second study in the same conditions as the first, which has not yet been published, comparing the dissolution profile of this formula with 2 lots of 2 other formulations, among which were included a flash release form, mouth-dispersible, which, when placed on the tongue rapidly dissolved in the mouth, releasing the microgranules contained inside the enteric covering (Figures 3 and 4; Tables 2 and 3). Once more, minimal differences were found in the dissolution profile between the intact and crushed forms, with the chewable formulation of calcium carbonate. The release of calcium from the tablet was also considerably more rapid with this formulation during the first hour, by which the speed of absorption and, possibly, the quantity of bioavailable calcium is higher in human beings.

5. Clinical evidence on its use

Supplements of calcium, combined with vitamin D should be considered for all people who: do not have an adequate ingestion of calcium, have oestopenia or osteoporosis, peri- and postmenopausal women, mothers in natural state of lactancy after a multiple birth, vegetarians, amenorrheic women, institutionalised older people, those intolerant of lactose, patients subject to chronic corticotherapy and who are suffering an inflammatory intestinal disease. Specifically, the association of calcium carbonate and vitamin D is indicated in: treatment of calcium and vitamin D deficiency in older people and as an adjuvant for specific treatment for osteoporosis in patients with risk of calcium and vitamin D deficiency.

During infancy and adolescence, it has been shown that the suboptimum supply of calcium is due to the replacement of the ingestion of milk with an excessive consumption of fizzy drinks[42]. In 2006, the American Academy of Pediatrics published a report which provided a guide for the optimisation of bone health in children and adolescents[43]. This report recommended the ingestion of daily sources of calcium, due to their prevalence in the diet, and other nutrients they contain. Supplementation is suggested as an alternative form to this daily food intake. In any case, a special emphasis is made for paediatricians to remind families of the benefits which calcium and vitamin D bring in the reduction of risk of suffering osteoporosis in the future, as well as suffering fractures during infancy and adolescence.

Calcium supplements can stimulate the growth of bone to a significant extent in young women[44]. In a randomised and controlled study or 4 years duration, 352 women at stage 2 of puberty were studied, this being the group in which the calcium supplements showed significant bone growth during the most accelerated phase of development. The authors conclude with the possible implication of these supplements in the prevention of osteoporosis and secondary fractures due to bone fragility during growth.

The need for calcium is exacerbated in menopause. The low levels of oestrogen favour bone resoprtion, at the same time as reducing the efficiency of the intestinal absorption of calcium and its renal conservation. At 65 years of age, the absorption of calcium is 50% of that seen in adolescence. An inadequate level of vitamin D may also limit the absorption of calcium and negatively

Figure 3. Dissolution profile of Mastical D© (Calcichew D_3©) and other reference products [Natecal D© (lots 06384 and 07073) and Natecal D Flas© (lots 08051 y 08057)] in the form of intact tablets. The composition of the 3 formulations is: vitamin D_3, 400 UI and calcium carbonate 500 mg for Mastical D© and 600 mg for Natecal D© and Natecal D Flas©).

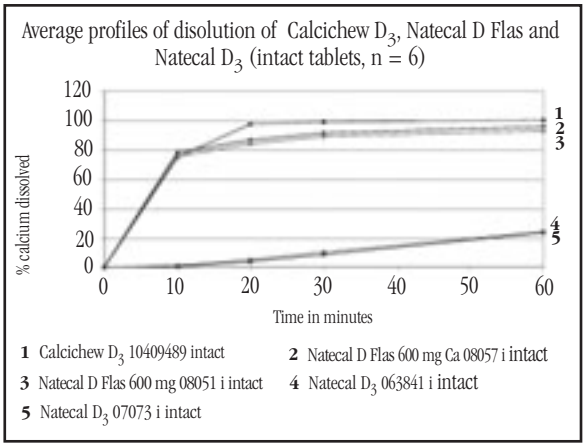
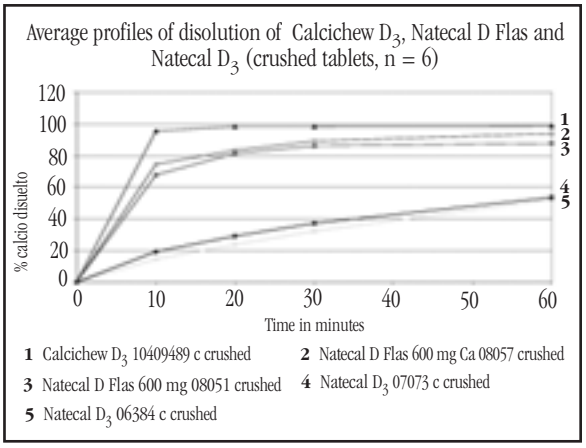


Figure 4. Dissolution profile of Mastical D© (Calcichew D_3©) and other reference products [Natecal D© (lots 06384 and 07073) and Natecal D Flas© (lots 08051 and 08057)] in the form of crushed tablets. The composition of the 3 formulations is: vitamin D_3, 400 UI and calcium carbonate, 500 mg for Mastical D© and 600 mg for Natecal D© and Natecal D Flas©).



affect bone health. With age, a number of factors contribute to its blood concentration being inadequate: inadequate intake, little exposure to the sun, reduction in the efficacy of renal transformation of vitamin D to 1.25 (OH) D and reduction in the intestinal response to vitamin D.

The North American Menopause Society (NAMS) recommends 1,200 mg of calcium daily and a sufficient supply of vitamin D, which allows blood levels of 25(OH)D ≥ 30 ng/ml. The primary source of calcium recommended is through food, but as alternatives supplements and reinforced foods are also recommended[45]. Calcium and vitamin D are recommended as adjuvants for all types of pharmacological treatments for osteoporosis. Clinical trials with calcium supplements, although of short duration, show a reduction in the loss of bone mass in women who are postmenopausal and at risk of fracture. A meta-analysis of 15 clinical trials which includes a total of 1,806 patients randomly allocated to calcium supplements or to its normal dietary intake over a period of 2 years shows an increase in bone density in the lumbar spine of 1.66%, 1.64% in the hip and 1.91% for the distal radius in the groups supplemented with calcium[46].

An analysis of 20 clinical trials in postmenopausal women also shows that supplementation with calcium (500-1,200 mg/day) reduces the annual loss of bone mass from 1% in women not receiving supplements to 0.014% in those receiving them[47].

A meta-analysis which includes 29 randomised clinical trials (n= 63,897) concludes that the evidence supports the use of calcium or calcium/vitamin D in the preventative treatment for osteoporosis in patients over 50 years of age. The reduction in risk of fracture is significant in those studies in which the degree of compliance of patients is highest. Also, the therapeutic effect is higher when a dose ≥ 1,200 mg/day of calcium and ≥ 800 UI/day of vitamin D is used[48].

Similarly, a double blind study controlled by placebo of 1,460 women over 70 years of age, followed for 5 years concluded that supplements of calcium carbonate at a dose of 1,200 mg/day, as means of public health intervention, are only efficacious in those patients who show a sufficient therapeutic compliance in the long term[49]. Beyond this, another meta-analysis of 7 prospective trials concludes that the intake of calcium alone, does not only demonstrate a reduction in risk of hip fracture, but that it may increase it[50].

The Women's Health Initiative (WHI), a long term randomised trial which studied more than 36,000 women of ages of between 50 and 79 years, over a period of 7 years, has assessed the effects of calcium and vitamin D on the prevalence of fractures[20]. The researchers have found a relative reduction of 29% (per protocol) in hip fractures in those women who complied daily with the treatment of 1,000 of calcium carbonate and 400 UI of vitamin D. Another interesting meta-analysis is that carried out on randomised clinical trials in patients (9,083) in whom oral vitamin D, with or without calcium supplements, was administered, when compared with a placebo. According to the results of the 4 clinical trials (9,083 patients), the balanced relative risk of hip fracture is 1.10 (CI 95%: 0.89-1.36) with monotherapy with vitamin D. For another 6 clinical trials (45,509 patients) with the calcium/vitamin D combination, the relative risk reduces to 0.82 (CI 95%: 0.71-0.94), which suggests that vitamin D only

Table 2. Percentage of calcium released in the dissolution study of Mastical D© (Calcichew D_3©) and other reference products [Natecal D© (lots 06384 and 07073) and Natecal D Flas© (lots 08051 and 08057)] in the form of intact tablets. The composition of the 3 formulations is: vitamin D_3, 400 UI and calcium carbonate, 500 mg for Mastical D© and 600 mg for Natecal D© and Natecal D Flas©).

	% calcium dissolved (average)		
Time (min)	**Mastical©**	**Natecal D©**	**Natecal D Flas©**
10	75.1	0.8-1.5	75.7-78.3
20	97.7	4.1-5.4	84.1-87.0
30	98.9	8.8-10.4	89.1-91.7
60	100.4	23.5-24.2	92.8-96.1
120	100.0		95.2-97.8

Table 3. Percentage of calcium released in the dissolution study of Mastical D© (Calcichew D_3©) and other reference products [Natecal D© (lots 06384 and 07073) and Natecal D Flas© (lots 08051 and 08057)] in the form of crushed tablets. The composition of the 3 formulations is: vitamin D_3, 400 UI and calcium carbonate, 500 mg for Mastical D© and 600 mg for Natecal D© and Natecal D Flas©)

	% calcium dissolved (average)		
Time (min)	**Mastical©**	**Natecal D©**	**Natecal D Flas©**
10	95.6	14.7-19.3	67.7-74.6
20	98.5	23.8-29.3	81.5-83.2
30	98.3	32.2-37.2	86.1-89.2
60	98.6	52.3-53.6	87.7-93.8
120	99.0		90.5-95.2

reduces the risk of hip fracture in association with calcium[51].

However, an additional effect which is found with an adequate supply of vitamin D is a reduction in the incidence of falls. Individuals with higher levels of 25(OH)D are able to walk and get up from a chair more quickly. These actions improve rapidly when the levels of 25 (OH)D increase from very low levels to the middle of the range of reference. The improvement continues, although more slowly, until the levels are at the higher limit of the said range[52,53].

More recently, at the 31st Annual Meeting of the American Society for Bone and Mineral Research, were revealed the results of a meta-analysis carried out on 5 European randomised clinical trials, in which it was concluded that calcium accompanied by vitamin D does not only reduce the mortality of older patients by diminishing the risk of hip fracture, but it even reduces the mortality within the group of patients who have already suffered one[54].

6. Conclusions

Calcium supplements play an important role in bone health throughout the cycle of life. For all those in whom we treat loss of bone mass, the aim is not only to ensure an adequate intake of calcium but also of vitamin D and other nutrients which are indispensible for bone health. The best way, from the pharmacological point of view, of supplementing calcium is in its carbonate form. Calcium carbonate is cost-effective, although it should be taken with meals, with the aim of optimising its bioavailability, and the dose for the most immediate absorption should not exceed 500 mg (which does not mean that this dose could be exceeded in preparations of sustained release). However, what should not be forgotten is the fact that there may be marked differences in the dissolution of the different preparations of calcium supplements, supposedly due to the pharmaceutical formulation, although not all the preparations of the same salt exhibit the same absorption.

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