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Effects of calcium and vitamin D, with and without lactulose, in bone mineral density on postmenopausal women with osteopenia: Pilot randomized controlled trial

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Summary

We report the results of a randomized, double-blind, double-dummy, multicenter, parallel group pilot study, the objective of which was to assess whether the addition of lactulose to vitamin D and calcium supplementation for 12 months contributed to bone mineral density (BMD) maintenance in postmenopausal women with osteopenia (T-score –1 to –2.5 SD). Women in the lactulose group (n=19) received lactulose 15 mL/day (equivalent to 10.05 g), vitamin D3 400 IU/day and calcium carbonate 500 mg/day, and women (n=22) in the placebo group were administered lactulose placebo, vitamin D3 400 IU/day and calcium carbonate 1,000 mg/day. The baseline daily calcium intake was similar in both study groups. The primary endpoint was the BMD in the lumbar spine at the final visit. A generalized liner model was used to assess final versus baseline differences in BMD in both study groups. Differences in least-square means of BMD between lactulose and placebo were not statistically significant both in the per-protocol data set (–0.012, 95% CI –0.031 to 0.007, P=0.224) and in the intention-to-treat population (–0.005, 95% CI –0.025 to 0.016, P=651). As we have not found differences within the two study groups, the addition of lactulose to 500 mg of calcium carbonate associated with vitamin D supplementation could have similar effects on lumbar BMD as 1.000 mg of calcium carbonate. These findings may indicate that lactulose may improve calcium absorption in postmenopausal women. A long follow-up study with a greater number of subjects would be necessary to confirm these preliminary observations.

Key words: *lactulose, calcium, bone mineral density, osteopenia, postmenopausal women.*

Introduction

Osteoporosis is a very common disease in postmenopausal women and people of an advanced age, and is associated with an increased risk of fractures. Fractures related to osteoporosis are a very significant public health problem, having a consequence of high rates of morbidity and mortality, as well as a reduction in the quality of the lives of those who suffer from it. In addition, its ever increasing incidence (due, in part, to the gradual aging of the population) has renewed interest in the efficacy and safety of drugs available for the treatment of the reduction in bone mineral density (BMD) associated with osteoporosis. An adequate intake of calcium and vitamin D plays a critical and synergistic role in the maintenance of optimum musculoskeletal health, and is considered to be the first step in the treatment of osteoporosis[1]. Numerous studies support the importance of vitamin D deficit as a risk factor for osteoporotic fractures, and the beneficial effects of a treatment which combines vitamin D (of 700 to 800 UI/day) and calcium (of 1,000 to 1,200 mg/day) in avoiding non-vertebral and hip fractures[2-8].

It has been shown that a fractional decrease in the absorption of calcium in older women with a low intake of calcium increases the risk of hip fracture[9]. The proportion of calcium absorbed through the intestine varies enormously, from 10% to 70%[10-12]. However, the availability of calcium in the bone depends more on intestinal absorption than on the amount of calcium ingested. Other factors apart from vitamin D, such as the amount of fat[13] and non-absorbable sugars[14] in the diet, stimulate the intestinal absorption of calcium. Hence, the non-digestible oligosaccharides (such as raffinose, stachyose, the fructo-oligosaccharides, the polydextrins, the insulins and lactulose) and the prebiotics in general have received increasing attention due to their selective effects on the intestinal flora, which have beneficial effects on the wellbeing of the host and their health[15,16].

Lactulose is a synthetic disaccharide. It is composed of molecules of galactose bonded to molecules of fructose by means of a beta-1-4 link. The compound is synthesised by the isomerisation of lactose. Lactulose is not produced naturally; the human body does not have enzymes capable of hydrolysing lactulose from the monosaccharides galactose and fructose. Lactulose passes through the gastrointestinal tract and reaches the colon not having been modified, where it is broken down into short chain fatty acids (AGCC) (lactic, acetic, propionic and butyric acids) through bacterial degradation. The bacterial transformation of lactulose into AGCC acidifies the contents of the colon and induces various physiological changes in the colon, which are responsible for the preventative and therapeutic effects of the lactulose in constipation, portosystemic encephalopathy, enteritis due to salmonella and other potential indications. In experimental studies, the acidification of the colon which results from the hydrolysis of lactulose increases the concentration of soluble calcium and the absorption of calcium mediated by vitamin D[17-22]. However, data obtained from clinical studies are scarce. In 12 postmenopausal women who participated in a randomised study, with double-blind crossing, the consumption over 9 days of lactulose increased the absorption of calcium with a dose-responsive effect[23]. In a clinical trial of double-blind design, randomised, with crossing, in 24 healthy adult male volunteers, lactulose increased the absorption indices of calcium and magnesium[24]. To our knowledge, there are no studies which have examined whether the potential impact of lactulose on calcium absorption results in an increase in BMD.

One of the secondary effects of calcium at normal doses used in the treatment of postmenopausal osteoporosis is the digestive intolerance which in many cases necessitates the withdrawal of the drug, or is a reason for the abandonment of treatment.

Hypothesis

The combination of lactulose (10 g), vitamin D (400 UI/day) and calcium carbonate (0.5 g/day) is the equivalent of a regular dose of calcium carbonate (1 g/day) plus vitamin D (400 UI/day), and has the same effect on BMD after 12 months of treatment, which would hypothetically reduce the possible secondary effects of high doses of calcium and would improve adherence.

Objectives of the study

The primary objective was to evaluate BMD in postmenopausal women with osteopenia after 1 year of treatment with a combined regimen of lactulose (10 g), vitamin D (400 UI/day) and calcium carbonate (0.5 g/day) with a calcium placebo, against a second regimen of the same dose of vitamin D and a double dose of calcium carbonate (1 g/day) with a lactulose placebo, administered over 12 months.

The secondary objectives were the BMD in the femoral neck and total hip, as well as the effect of the treatment on the analytical parameters for bone remodelling, specifically, changes in the levels of blood calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D and the urinary secretion of calcium, as well as changes in the values of bone alkaline phosphatase, blood CTx, and urinary NTx over the period of the study.

Subjects and methods

Design of the study

It consisted of a pilot prospective trial, phase IV, randomised, double blind, double simulation, of parallel groups. The study was carried out in the external clinics of the rheumatology and internal medicine services of two university hospitals with bone mineral metabolism units in Barcelona (Spain). The duration of the study was 12 months. Approval for the study was obtained from the national health authorities and from the committees for ethics and clinical trials of the participating hospitals. All the women gave their informed consent in writing.

Table 1. Baseline characteristics of the population of study (ITT population data)

	All women n=41	Study groups	
		Lactulose, n=19	Placebo, n=22
Age, years. Average (min-max)	58.5 (52-67)	57.6 (52-67)	59.4 (55-67)
Weight, kg. Average (min-max)	70.2 (52-110)	70.0 (56-110)	70.4 (52-90.5)
Height, cm. Average (min-max)	156.7 (144-169)	154.6 (144-163)	158.4 (146-169)
BMI, kg/m^2. Average (min-max)	28.6 (21.2-47.6)	29.4 (23.3-47.6)	28.0 (21.2-32.9)
Smoker			
Non-smoking	31 (75.6)	13 (68.4)	18 (81.8)
Former smoker	4 (9.8)	3 (15.8)	1 (4.5)
You smoke now	6 (14.6)	3 (15.8)	3 (13.6)
Physical exercise	36 (87.8)	18 (94.7)	18 (81.2)
Take a walk	32	17	15
Swim	4	3	1
Other	9	6	5
No exercise	5	1	4
Average food consumption, (SD)			
Dairy products, g/day	381.7 (206.9)	444.9 (251.1)	325.5 (142.7)
Total calcium, mg/day	698.7 (376.3)	825.8 (469.9)	585.8 (226.8)
Concomitant medication	36 (87.8)	17 (89.5)	19 (86.4)
Anti-inflammatory drugs	20	12	8
Pain relievers	17	6	11
Angiotensin renin inhibitors	11	8	3
Psychos-Analeptics	11	7	4
Psycholeptics	8	3	5
Lipid-lowering agents	6	3	3
Antacids	4	1	3
Antimicrobial	4	2	2
Beta-blockers	3	1	2
Calcium channel blockers	3	2	1
Mineral supplements	3	2	1
Other	17	8	9

Data such as numbers and percentages in parentheses unless stated otherwise.
ITT: intention-to-treat; SD: standard deviation.

Study population

Between June 2003 and March 2006 postmenopausal women between 50 and 70 years of age having had amenorrhea for a minimum of 5 years and osteopenia defined as BMD with a T-score of between -1 and -2.5 in the lumbar spine (L2-L4), and/or femoral neck or total hip were recruited[25]. The exclusion criteria were: suffering from any disease which would cause osteopenia or alterations in the metabolism of calcium or phosphorus, or any disease in which the taking of calcium and vitamin D or the use of laxatives were contraindicated; presence of galactosemia; treatment with corticosteroids, antacids which contain calcium, iron salts, or thiazides; continuing treatment with lactulose; treatment with vitamin D and/or calcium

supplements in 4 weeks prior to the study, or treatment with antiresorptives (bisphosphonates, hormone replacement therapy, raloxifene, etc.); known hypersensitivity to the drugs used in the study; serious illness, substance abuse, serious neurological disorders, psychiatric disease, or any disease which, in the opinion of the researcher could mean that the patient might not sufficiently comply with the protocol of the study.

Evaluation of bone mass and laboratory parameters

A pre-study visit (visit 1) was carried out in the month prior to the randomisation, which included: anamnesis and complete physical examination, evaluation of the intake of calcium, physical exercise and concomitant medicines, laboratory and bone densitometry tests. The evaluation of the calcium intake was carried out by means of a survey of the number of daily and weekly portions of different types of foods which were consumed (milk products, cereals, fruits, vegetables, fish and meat). Samples of blood and urine were obtained from all patients, at between 8 and 10 in the morning, after 12 hours of fasting. The laboratory tests included standard biochemical and haematological profiles, blood levels of calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D, and urinary secretion of calcium (urine in 24 hours). In addition, the following markers for bone remodelling were measured: bone alkaline phosphatase, C-terminal telopeptide of type 1 collagen in blood (CTx) and N-terminal telopeptide of type 1 collagen in blood (NTx) (second sample of urine). To measure BMD in the femoral neck and total hip a Hologic® QDR-4500 (Hologic, Waltham, MA, US.) bone densitometer was used. The results were expressed in g/cm^2 (coefficient of variation of 1.3% in the lumbar spine and 1.65% in the femoral neck) and as T and Z score values.

In visit 2, after confirming the women's criteria of inclusion, no more than one month after visit 1, the two treatments of the study were assigned sequentially in a 1:1 proportion per treatment group using a centralised, computer-randomised list. The treatment administered in the lactulose group was: lactulose (Duphalac®, Solvay Pharma, Barcelona, Spain) (15 mL equivalent to 10.05 g), vitamin D_3 (colecalciferol) (400 IU/day), calcium carbonate (250 mg, twice a day) and placebo of calcium (250 mg, twice a day). The women assigned to the placebo group received a placebo of lactulose (15 mL), vitamin D_3 (400 UI/day) and calcium carbonate (500 mg, twice a day). It was recommended that the lactulose (or the lactulose placebo) be taken diluted in water or other appropriate liquid (orange juice, coffee, tea) and the placebo of calcium carbonate during dinner. The medications for the study were supplied to the subjects at the initial visit to cover the subsequent 3 months of the study.

The follow up visits were carried out at 30 days (visit 3), at six months (visit 4) and at 12 months (visit 5) after the initiation of the treatment. At the follow up reviews anamnesis, a complete physical examination, laboratory tests, and evaluation of concomitant medication and of adverse events were carried out. Compliance and adherence to the treatment were evaluated by means of a questionnaire and by counting the medicine used. A measurement of the women's BMD was made at 6 and 12 months (visits 4 and 5).

Parameters of efficacy and safety

The safety parameters were the incidence and gravity of adverse effects during the period of the study, measurement of vital signs, monitoring of complete blood count and blood biochemistry.

Statistical analysis

Due to the lack of previous studies which evaluated the efficacy of lactulose combined with vitamin D and calcium to conserve BMD in postmenopausal women, a sample size of 40 subjects was established for this pilot clinical trial, including abandonments and losses. The ITT population was defined as all the randomised women who had received at least one dose of medicine and who had BMD data available after the randomisation. The method was that the last observation registered was used to replace lost values. The PP population was defined as all those randomised women who complied with the inclusion/exclusion criteria, who had received the medicine being studied and who finished the trial as it was established in the protocol. The safety population included all those randomised subjects who received at least one dose of the drug in the study.

Different parametric and non-parametric statistical tests were used, such as Student's t-test, the Mann-Whitney U test, the Kruskal-Wallis test, the Wilcoxon test, the chi-squared test (χ^2), Fisher's exact test or Friedman's variance analysis (ANOVA) according to their correspondence. The analysis of the primary objective was carried out with the data of the PP population. The primary analysis was the difference between the values of BMD (L2-L4) between visit 1 (initial) and visit 5 (end of study) in both treatment groups. The differences in the measurement of BMD between the lactulose and placebo groups were analysed using a general linear regression model (ANCOVA), in which the value of BMD at visit 5 was the dependent variable, the value of BMD from initial measurements was the covariable (ANCOVA), and the treatment received, a fixed effect. The 95% confidence interval (CI) was calculated for the difference between the final and initial values of BMD. The primary endpoint was also analysed in the ITT population to confirm the results obtained in the PP population. The statistical significance was set at $p < 0.05$. For the analysis of data, the Statistical Analysis System (SAS Institute, Cary, NC, EE.UU. (version 9.1)) was used.

Results

Of the 68 potential participants, 21 did not comply with an inclusion criterion. Of the 47 remaining women included in the safety population, 6 were

Table 2. Results of bone densitometry measurements in PP and ITT populations

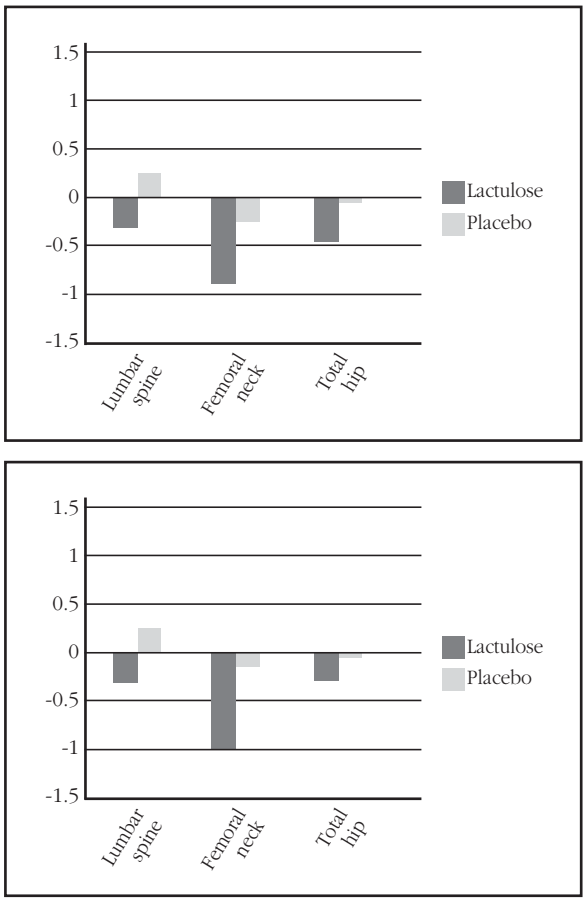
	Lactulose	Placebo
Population PP. Nº	**16**	**19**
BMD (L2-L4), g/cm². Average (SD)		
Visit 1 (commencement)	0.904 (0.058)	0.920 (0.082)
Visit 4 (6 months)	0.903 (0.057)	0.924 (0.088)
Visit 5 (at 12 months)	0.893 (0.064)	0.922 (0.092)
Change of the visit 1 to 5. %	-0.306	0.262
BMD FN, g/cm². Average (SD)		
Visit 1 (commencement)	0.753 (0.062)	0.732 (0.051)
Visit 4 (6 months)	0.744 (0.060)	0.725 (0.054)
Visit 5 (at 12 months)	0.746 (0.067)	0.730 (0.06)
Change of the visit 1 to 5. %	-0.884	-0.267
BMD CT, g/cm². Average (SD)		
Visit 1 (commencement)	0.897 (0.068)	0.869 (0.067)
Visit 4 (6 months)	0.887 (0.073)	0.874 (0.65)
Visit 5 (at 12 months)	0.893 (0.076)	0.869 (0.071)
Change of the visit 1 to 5. %	-0.447	-0.002
Population ITT. Nº	**19**	**22**
BMD (L2-L4), g/cm². Average (SD)		
Visit 1 (commencement)	0.934 (0.104)	0.922 (0.083)
Visit 4 (6 months)	0.938 (0.11)	0.928 (0.092)
Visit 5 (at 12 months)	0.912 (0.083)	0.929 (0.092)
Change of the visit 1 to 5. %	-0.306	0.262
BMD CF, g/cm². Average (SD)		
Visit 1 (commencement)	0.749 (0.062)	0.726 (0.049)
Visit 4 (6 months)	0.743 (0.064)	0.723 (0.05)
Visit 5 (at 12 months)	0.747 (0.065)	0.727 (0.057)
Change of the visit 1 to 5. %	-0.990	-0.157
BMD TC, g/cm². Average (SD)		
Visit 1 (commencement)	0.896 (0.074)	0.876 (0.065)
Visit 4 (6 months)	0.892 (0.079)	0.880 (0.063)
Visit 5 (at 12 months)	0.901 (0.079)	0.74 (0.069)
Change of visit initial at the end. %	-0.273	-0.084

Visit 1: pre-treatment; visit 4: six months of treatment; visit 5: 12 months of treatment (end of study).
PP: data by protocol; ITT: data by intention to treat; SD: standard deviation; FN: femoral neck; TH: total hip.

excluded from the analysis of efficacy since it was not possible to carry out the second measurement of BMD. In the ITT population were included 41 women, 19 allocated randomly to the lactulose group and 22 to the placebo group. Six women did not complete the study: two due to infractions of the inclusion criteria, three withdrew due to the appearance of adverse events and one due to there not being enough medication. Therefore, 35 women, 16 in the lactulose group and 19 in the placebo group, completed the study and were included in the PP data.

The average age of the women was 58.5 years (between 52 and 67 years of age) and the average body mass index (BMI) was 28.6 kg/m² (between 21.1 and 47.6 kg/m²). The total intake of calcium

Figure 1. Evolution of BMD in the lactulose and placebo groups between the initial visit and that at 12 months, in the PP (upper panel) and ITT (lower panel) populations. (Data expressed as percentage change)



was 698.7 (± 376.3 SD). The intake from milk and milk-derived products was 381.7 mg/day (± 206.9 SD), from cereals 50.4 mg/day (± 29.5 SD), from fruit 160.7 mg/day (± 72.1 SD), from fish 62.9 mg/day (± 82.9 SD) and meat 15.7 mg/day (± 9.4 SD). No patients declared having consumed more than 40 g/day of alcohol, and only 6 women were smokers during the study. Concomitant medication was recorded in 87.8% of the women, the most frequent being: non-steroid anti-inflammatories, analgesics, and hypotensives (Table 1). There were no statistically significant differences in these values between the two groups.

Efficacy

The results of the measurements of BMD in L2-L4, in the femoral neck and in the total area of the hip at the initial visit and after 6 and 12 months of treatment are shown in Table 2. The results were similar in both PP and ITT populations.

In terms of the measurement of the results of the main objective in the PP analysis, the minimum mean square (standard error – SE) for the difference in BMD in the lumbar spine (l2-L4) between that at 12 months and that at the initial stage was 0.902 (0.007) for the lactulose group, and 0.914 (0.006) for the placebo group; the difference between the two groups was -0.012 (95% CI, -0.031 to 0.007; p=0.224). The analysis of the ITT data gave similar results, with the minimum mean square for BMD of 0.917 (0.007) and 0.921 (0.007) in the lactulose and placebo groups respectively, p=0.652) (Figure 1).

With respect to the secondary objectives, no statistically significant differences were observed between the lactulose and placebo groups. In the PP data, the minimum mean square (SE) for the difference in BMD in the femoral neck between visits 5 and 1 was 0.734 (0.006) for the lactulose group and 0.740 (0.006) for the placebo group; the difference between the two groups was -0.006 (95% CI, -0.024 to 0.012; p=0.493). The analysis of the ITT data showed a minimum mean square (SE) of 0.731 (± 0.006) and 0.739 (± 0.005) in the lactulose and placebo groups respectively, and a difference between the two groups of the study of -0.008 (95% CI, -0.024 to 0.008; p=0.298). On the other hand, the measurement of BMD in the total hip showed a minimum mean square (SE) of 0.878 (0.005) and 0.882 (0.005) in the lactulose and placebo groups for the analysis of PP data (difference of –0.005, 95% CI, –0.019 to 0.009; p=0.485), and 0.885 (0.005) and 0.889 (0.004) in the lactulose and placebo groups for the analysis of ITT data (difference of –0.004, 95% CI, –0.016 to 0.009, p=0.565).

The changes in analytic parameters for the markers for bone remodelling are shown in Table 3. There were no statistically significant differences between the lactulose and placebo groups in the initial and final values of the study. All the parameters were within normal limits. The percentage change in blood calcium, in phosphorus, in bone alkaline phosphatase, in parathyroid hormone, in urinary calcium and in NTx after 12 months of treatment in the lactulose and placebo groups were not statistically significant. The percentage change in CTx in the lactulose group was not significant, but in the placebo group the average percentage change was – 13.3 ± 0.3 SD (p=0.046). The levels of 25-hydroxyvitamin D increased considerably in the lactulose group (percentage change of 41.4 ± 10.6 SD, p=0.006) and in the placebo groups (percentage change of 35.4 ± 10.7 SD, p=0.003).

No differences were observed in physical exercise or in consumption of milk products, nor in calcium derived from milk products, cereals, fruit, meat and fish in the data recorded for initial and final values for the study.

Safety

A total of 12 women (50%) from the lactulose group and 14 (60.9%) in the placebo group confirmed that they had suffered light adverse events. Only 7 women (3 in the lactulose, and 4 in the placebo group) reported having had more than two adverse events. The most common adverse events were: abdominal distension, urinary tract

Table 3. Changes in analytical parameters for bone metabolism in the two groups over the period of the study

	Initiation		At 6 months		At 12 months	
	Lactulose	Placebo	Lactulose	Placebo	Lactulose	Placebo
Calcium, mg/dL	9.1 (0.6)	9.3 (0.5)	9.2 (0.4)	9.2 (0.4)	9.3 (0.4)	9.1 (0.4)
Phosphorus, mEq/L	3.5 (0.3)	3.6 (0.7)	3.6 (0.4)	3.4 (0.4)	3.6 (0.4)	3.3 (0.4)
Bone alkaline phosphatase, ng/mL	12.3 (5.7)	11.7 (3.6)	11.9 (5.2)	10.9 (2.4)	12.9 (6.0)	11.4 (2.9)
CTx, ng/mL	0.4 (0.2)	0.5 (0.3)	0.3 (0.1)	0.3 (0.1)	0.3 (0.2)	0.3 (0.2)
Parathyroid hormone, pg/mL	48.9 (21.9)	46.6 (14.6)	51.8 (21.8)	48.1 (14.7)	47.6 (18.2)	41.2 (13.2)
25-hydroxyvitamin D, ng/mL	25.8 (7.6)	23.3 (8.0)	33.0 (8.5)	32.1 (7.6)	34.4 (9.8)	30.4 (9.6)
Urine calcium, mg/24 h	231.0 (159.8)	217.5 (130.5)	207.3 (127.1)	213.4 (89.8)	226.3 (117)	268.3 (94.9)
NTx, nM/mM	45.8 (13.8)	52.5 (26.1)	38.1 (10.3)	38.3 (14.5)	40.9 (13.4)	43.3 (17.5)

Data expressed as mean and (SD).

infection, back pain and arthralgia. The distribution of the adverse events by organ class and system were similar in both groups of the study. Three women discontinued the treatment at visit 4 due to these adverse events, which included a period of constipation which persisted after having stopped taking the treatment being studied in a patient assigned to the placebo group, and an episode of gastroenteritis and diarrhoea in two women assigned to the lactulose group. In the three cases the adverse events were of moderate intensity and possibly related to the drugs being studied. There were no serious adverse events or deaths during the study.

No significant changes in vital signs, or in the results of the laboratory tests, were observed. Adherence to the medication being studied was sufficient in 84.7% of the women in the lactulose group and 89.9% in the placebo group (p=0.685).

Discussion

Lactulose is a drug very commonly used in this population (postmenopausal women) as a laxative, with few secondary effects, and which may be of interest due to the effect of improving the intestinal absorption of calcium which it is known to produce[23,24]. This study is the first which has evaluated the effect of lactulose on BMD in osteopenic postmenopausal women. No differences were found between the two study groups, from which is may be concluded that the addition of lactulose to the 500 mg of calcium carbonate associated with vitamin D supplements could have a similar effect on lumbar BMD as 1,000 mg of calcium carbonate. Therefore, the results of this study can support the possible beneficial effects of this prebiotic non-digestible disaccharide on the maintenance of BMD, reducing the necessary dose of calcium. It is important to stress that this was a pilot study designed to detect possible changes, and that one of its limitations is the relatively small number of women and the short duration of the study. However, the results do show the maintenance of BMD. On the other hand, the combination of lactulose, vitamin D and calcium was well tolerated, and the safety profile in both groups was similar.

In terms of the possible mechanism through which the bone mass would be preserved in the women treated with lactulose, this may be related to an increase in the absorption of calcium. This is not possible to confirm conclusively, since the absorption of calcium was not really measured directly, for example, with the use of isotopic techniques. An indirect measurement is the urinary excretion of calcium, and in the study no significant changes were found in this parameter. In any case, it has been confirmed that the absorption of calcium induced by non-digestible oligosaccharides is not accompanied by a greater urinary excretion of calcium, which means that these compounds may also increase indirectly the reception of calcium by bone and/or inhibit bone resorption[14]. Consequently, not having found increases in the urinary excretion of calcium, does not weaken speculation that this is the mechanism involved in the maintenance of BMD found in this study.

An important point to note is that blood levels of 25-hydroxyvitamin D increased significantly in both groups in the study as a consequence of the vitamin D supplement, but with a higher tendency in the lactulose group. This observation may have clinical significance due to the low intake of calcium and vitamin D deficiency which a high percentage of postmenopausal women exhibit[25,26]. However, the effect lactulose or other prebiotics have on the absorption of vitamin D has not previously been investigated. In relation to the biochemical markers for bone turnover, no significant differences were found in the values of bone alkaline phosphatase in the blood, or in NTx in urine, in either of the two groups. However, the values of CTx were significantly lower at the end of the study in the placebo group, although the magnitude of the change was very modest (11%). Together, these results are similar to those observed in most of the studies with drugs for osteoporosis, when the placebo arm which included supplements of calcium and vitamin D are analysed. Thus, the changes in the placebo group of the sub-study of the Fracture Intervention Trial (FIT) and Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) studies showed modest reductions in values of bone alkaline phosphatase, which were 14% a year in the FIT study, or similarly non-significant reductions for bone alkaline phosphatase and CTx in the FREEDOM sub-study[27,28].

This pilot study suggests that, in postmenopausal women with osteopenia, the addition of 10 g/day of lactulose to 500 mg of calcium plus vitamin D, over 12 months, showed no differences in the conservation of bone mass from a supplement of 1,000 mg of calcium carbonate plus vitamin D. It would be necessary to conduct a study which was longer and had a greater number of subjects in order to be able to confirm these preliminary observations.

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