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Estudio del efecto del tratamiento con denosumab en la osteoporosis por hiperparatiroidismo primario

Escribir Título TFG en Inglés

Study of the effect of treatment with denosumab in osteoporosis due to primary hyperparathyroidism

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RESUMEN

El hiperparatiroidismo primario consiste en la hiperfunción de una o varias glándulas paratiroideas con producción suprafisiológica de parathormona (PTH) que no es adecuadamente inhibida por el calcio sérico. Una de sus principales complicaciones es la osteoporosis, siendo la hiperparatiroidectomía el tratamiento más eficaz para prevenirla. No obstante, aquellos pacientes que o bien no son candidatos a cirugía, o bien son refractarios a la misma, pueden beneficiarse de tratamiento farmacológico adicional. Entre los fármacos propuestos para tratar la osteoporosis se encuentra el denosumab. Aunque se ha estudiado ampliamente para la prevención de fracturas en la osteoporosis primaria, menos evidencia hay sobre su uso para la osteoporosis secundaria por hiperparatiroidismo primario. Hemos realizado un estudio de casos y controles definiendo caso como aquellos pacientes que recibieron denosumab y control como aquellos pacientes que habían sido operados o bien habían recibido tratamiento con bifosfonato. Al finalizar el seguimiento, aquellos pacientes que recibieron denosumab no sufrieron más fracturas que los controles aunque sí que hubo una ligera tendencia a perder más densidad mineral ósea. Denosumab parece ser una opción terapéutica efectiva en la prevención de fracturas en aquellos pacientes con osteoporosis secundaria a hiperparatiroidismo primario.

***Palabras clave**:* “Hiperparatiroidismo primario”, “denosumab”, “bifosfonatos” “paratiroidectomía”, “osteoporosis”

ABSTRACT

Primary hyperparathyroidism consists of hyperfunction of one or more parathyroid glands with supraphysiological production of parathyroid hormone (PTH) that is not adequately inhibited by serum calcium. One of its main complications is osteoporosis, and hyperparathyroidectomy is the most effective treatment to prevent it. However, patients who are either not candidates for surgery or are refractory to it may benefit from additional pharmacological treatment. Among the drugs proposed to treat osteoporosis is denosumab. Although it has been widely studied for the prevention of fractures in primary osteoporosis, there is less evidence for its use in secondary osteoporosis due to primary hyperparathyroidism. We have carried out a case-control study defining case as those patients who received denosumab and control as those patients who had undergone surgery or had received bisphosphonate treatment. At the end of the follow-up, those patients who received denosumab did not suffer more fractures than the controls, although there was a slight tendency to lose more bone mineral density. Denosumab appears to be an effective therapeutic

option in the prevention of fractures in those patients with osteoporosis secondary to primary hyperparathyroidism.

Key words: “Primary hyperparathyroidism”, “denosumab”, “bisphosphonates”, “parathyroidectomy”, “osteoporosis”

INTRODUCTION

Pathophysiology

Primary hyperparathyroidism (PHPT) is defined as an inadequately high secretion of parathormone (PTH) from one or more parathyroid glands in the absence of any other cause for PTH elevation. Although some patients with PHPT may have normal serum calcium concentrations, most have hypercalcemia. The principal regulators of PTH secretion are extracellular ionized calcium (Ca2+) and 1,25-dihydroxyvitamin D (1,25(OH)2D). Other potentially important regulators include serum phosphate and fibroblast growth factor 23 (FGF23). A rise in extracellular ionized calcium levels activates the calcium-sensing receptor (CASR), which suppresses PTH expression. However, this regulation is lost in patients who suffered primary hyperparathyroidism, in whom high serum calcium concentration cannot inhibit PTH secretion(1).

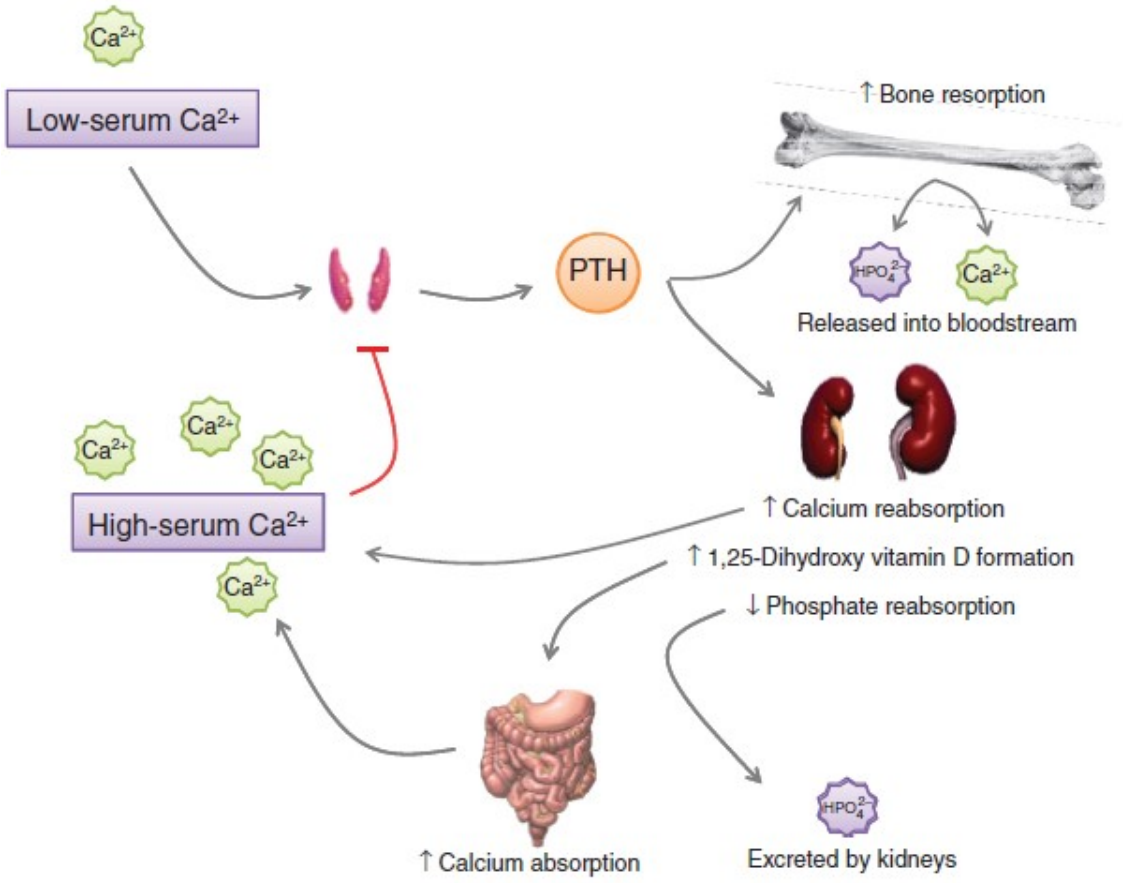
PTH is the key hormone in the regulation of extracellular calcium, raising its serum levels by acting on several systems(2):

At the renal level, it favors calcium absorption in the proximal tubule while it decreases phosphorus absorption. It also elevates the conversion of 25-hydroxycholecalciferol in the kidney to its active form, 1,25-dihydroxycholecalciferol.

At the digestive level, it indirectly increases the absorption of calcium and phosphorus by increasing the activity of the enzyme 1-alpha-hydroxylase.

At the bone level, it increases bone resorption, thus raising the levels of calcium, phosphorus and magnesium. Note that PTH promotes bone anabolism when used intermittently; whereas persistently high concentrations have a catabolic effect on bone, as appears in hyperparathyroidism. The physiology of PTH is summarized in Figure 1.

Figure 1. Regulation of serum Ca^{2+} by PTH in healthy subjects. Extracted from Syed Jalal Khundmiri et al(2).



As stated previously, the most potent inhibitor of PTH secretion is ionic calcium. Another known inhibitor is 1,25-dihydroxycholecalciferol. On the other hand, elevated phosphorus increases serum PTH concentrations, partly explaining the secondary hyperparathyroidism that appears in chronic renal failure(3).

Epidemiology

A study from 2012 made in Spain(4) reported an incidence of PHPT of 9.95/100,000 person-years with a reported prevalence of 22.4/100,000, being the most patients asymptomatic at the time the diagnosis was made. It affects more often women than men. Although the curative treatment is parathyroidectomy, not all patients accomplish criteria to include in a surgery

program. In the previous study, the main criteria for parathyroidectomy were T-score ≤-2.5 standard deviations at any side (90.9%) followed by a glomerular filtration rate <60 ml/min (81.%); while the main reason for not performing the surgery was medical contraindication followed by patient's refusal.

Clinical presentation

As stated above, the most frequent clinical presentation in our environment is incidental after performing an analysis for another reason. Less frequently it appears in the study of osteoporosis or renal lithiasis. Most of the time, the aetiology is sporadic, with no risk factor or familial predisposition being able to be identified. Known risk factors include exposure to ionizing radiation in childhood, treatment with lithium or thiazides therapy(5). It rarely appears as part of a multiple endocrine neoplasia (MEN), such as MEN1, MEN2A or MEN4. This last group of syndromes should be suspected when PHPT appears in young patients, accompanied by hyperfunction of other endocrine systems or in case of a family history of MEN since it has autosomal dominant transmission(6).

Diagnostic criteria

Regarding the diagnostic criteria, combination of hypercalcemia and an elevated or inappropriately normal concentration of PTH in an absence of secondary causes is diagnostic of PHPT(7). Other forms include normal serum normalized-calcium with elevation of ionized normalized calcium or normocalcemic primary hyperparathyroidism. Several hypotheses have been formulated to explain this phenomenon.

Normocalcemic hyperparathyroidism may represent an incipient PHPT that will eventually develop into hypercalcemia. It can also mean calcium elevation of 1mg/dL in people who normally manage concentrations around 9mg/dL, resulting in normal serum calcium of 10mg/dL for a patient who had lower calcium concentrations in the past, but still are in the normal population range(8).

Role of imaging test

The main utility of imaging tests is to shorten the time of surgery as well as to avoid removing healthy glands. Therefore, its indication is as a preoperative study in patients who meet the criteria for inclusion on the surgical waiting list. Several imaging tests have been studied to estimate their diagnostic value. 99 mTc methoxyisobutylnitrile (MIBI) parathyroid scintigraph has a sensitivity of 90.9% and a specificity of 98.06% for locating an adenoma, while it has a sensitivity of 85.3% and a specificity of 91.11% for locating a gland hyperplastic. On the other hand, ultrasound has a sensitivity of 87.1% and a specificity of

88.24% to locate an adenoma, but a sensitivity of 72.5% and specificity of 75.56% to locate a hyperplastic gland. The combination of the two tests increases the sensitivity in the first case to 96.9% and in the second to 90.4%. The parameter that best predicts a positive imaging test is the weight of the gland, followed by PTH levels, being the most frequent finding a solitary adenoma(9).

Complications and treatments

Individuals with PHPT are at great risk from suffering osteoporosis and nephrolithiasis. At presentation, 9.7% patients have an established diagnosis of nephrolithiasis and 48.4% had a diagnosis of osteoporosis based on conventional WHO T-score criteria(10). To avoid complications such as osteoporosis, not only parathyroidectomy is the definitive treatment(11), but it is also the most cost-effective treatment(12). The surgical criteria most widely accepted by the scientific community are those set out by National Institute for Health consensus guideline(13):

- Serum calcium (>upper limit of normal): 1.0 mg/dL (0.25 mmol/L).
- BMD by DXA: T-score ≤2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius.
- Vertebral fracture by x-ray, computed tomography scan or magnetic resonance imaging.
- Creatinine clearance <60 cc/min; 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis
- Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or computed tomography
- Twenty-for-hour urine calcium >400mg/day.
- <50 years

An alternative to surgery in patients at high surgical risk is the enolization of the hyperfunctioning gland. The main disadvantage is that it has a higher risk of recurrence compared to standard surgery. However, it is an option to consider in non-operable elderly patients(14). Prospective follow-up studies have demonstrated that surgery helps recovering bone mass lost (15), but some patients may need pharmacological therapy besides surgery in order to treat osteoporosis. Main drugs approved for primary osteoporosis are denosumab, teriparatide and bisphosphonates(16).

Denosumab is a new human monoclonal antibody against Receptor activator of nuclear factor κ B (RANK) ligand. RANK is a receptor that plays a key factor in bone mass metabolism. It is mainly expressed in osteoclasts and brain regions associated with thermoregulation, in which RANK-L injection raise body temperature(17). It is thought that menopausal hot flashes are linked with the estrogen depletion at menopause(18) by inducing osteoprotegerin expression,

an important inhibitor of RANK / RANK-L pathway(19). RANK / RANK-L role in bone mass metabolism consists in activate osteoclast activity, which leads to accelerate bone resorption(20). On the other hand, osteoblasts are the cells that synthesize bone. A misbalance between osteoblasts and osteoclasts function leads to a decrease in bone mass, the main mechanism for whom osteoporosis is developed(21). Therefore, RANK-L inhibitors, such as denosumab, blocks RANK-L signalling inhibiting osteoclast activity, enhanced bone density. It has demonstrated that twice yearly subcutaneous injection stops bone resorption, proving to be an efficacy option to treat osteoporosis(22). After the first injection of denosumab, it is expected that PTH levels will increase transiently, but it is not known if this has clinical relevance(23). Although it is well tolerated, several adverse effects have been reported.

RANK-L route plays a role in lymphoid tissue organogenesis, development of T and B lymphocytes, and formation of the thymus, so denosumab may also act as a mild immunosuppressant agent. It has been proven that patients receiving denosumab are at higher risk of developing gastrointestinal infections and otorhinolaryngological infections, but with no effect in mortality(24,25). No evidence has been found that patients treated with denosumab are at risk for more severe COVID-19 infection. (26)

Another side effect to be taken into account is hypocalcemia. A long follow-up cohort study shows a 7’4% rate of mild hypocalcemia and 1% of severe hypocalcemia(27). As bone resorption increases serum calcium levels, its inhibition is expected to decrease its concentration. This effect is dose-dependent, and more frequent in individuals who suffer from vitamin D and calcium deficiency or have high serum concentrations of alkaline phosphatase. In addition, dialysis patients are at increased risk from suffering this side effect, because the regulatory action of the kidneys on mineral metabolism is lost(28). It is therefore highly recommended that all patients treated with denosumab receive daily supplementation with at least 500 mg calcium and 400 IU vitamin D, unless hypercalcemia is present. (29)

The most serious side effect is osteonecrosis of the jaw (ONJ). Fortunately, it is extremely rare in patients with no risk factors. Dental extraction, poor oral hygiene, and chemotherapy treatment are situations that increases the possibilities of developing ONJ(30). Its treatment is complex, and includes surgery and antibiotic therapy. Recently, teriparatide has been shown to improve the rate of resolution of this severe side effect(31).

It is important to note that discontinuation of denosumab greatly increases the risk of fracture; therefore, it is highly recommended to prescribe a bisphosphonate after its withdrawal(32).

Bisphosphonates are a family of drugs that inhibit farnesylpyrophosphate synthase, which leads to a decreased function of the osteoclasts. Moreover, they also work in osteoblasts and osteocytes activating anti-apoptotic signalling pathways. As a result, they increase bone mass density. Some of them are available as oral therapy (alendronate, risedronate and ibandronate), while zoledronic acid is reserved to intravenous infusion(33).

They are commonly used for osteoporosis(34), although they are also highly effective in Paget's disease(35), or multiple myeloma. Note that those patients with multiple myeloma who receive bisphosphonates have the highest risk of developing ONJ, reaching the number of 1/1000 treated(36).

All patients taking oral bisphosphonates should be warned about the risk of developing esophagitis and other digestive complaints. To reduce the risk, all patients should take the medication with plenty of water and remain standing or sitting for the next half hour(37).

Although both treatments have been well studied for primary osteoporosis, there is less evidence of their use for osteoporosis secondary to PHPT. We are going to focus on how these treatments can help in secondary osteoporosis due to PHPT.

OBJECTIVES

The primary objective of this work is to evaluate whether denosumab prevents the decrease in BMD and prevents the appearance of fractures in patients with PHPT. The secondary objective is to assess whether denosumab is capable of preventing other PHPT-related complications such as nephrolithiasis or hypercalcaemia.

METHODS

Patient Selection

Data were extracted from medical records of 73 patients from University Hospital “Marqués de Valdecilla” who met the following inclusion criteria: (1) A clear diagnosis of PHTP, (2) women, (3) at least 20 months of follow up (4) and a densitometry before and after treatment.

Study design

We conducted a case-control study based on the population previously selected. Case definition includes patients who were treated with denosumab. A total of 17 patients were included in this category.

Control definition includes patients who underwent parathyroidectomy during follow-up period or were treated with bisphosphonates. A total of 56 patients were included in this category. We tried to match controls to cases as much as possible regarding age and glomerular filtration.

Study variables

Demographic variables included age. Clinical variables included body mass index, albumin-corrected calcium, normalized ionic calcium, serum phosphorus, serum magnesium, glomerular filtration, 24 hour calciuria, PTH levels, vitamin D levels, densitometry of the lumbar spine, neck of the femur, total femur and distal third of the radius. Therapeutic variables included any drug that could interfere in bone mass (corticoids, bisphosphonates, hormone therapy or teriparatide), and if they underwent parathyroidectomy before and during follow-up.

Statistical analyses

Descriptive analyses were carried out for all basic characteristics and mean ± SD was calculated for all of them. We checked that all variables had a normal distribution and then we performed a Student's t-distribution for independent quantitative variables comparing the case group with the control group. We have performed a Chi-squared test for comparing qualitative variables.

RESULTS

At baseline, the mean age of the case group was 75,71 ± 6,93, years while the mean age of the control group was 62,90 ± 11,77 ($p<0,0001$). Normalized serum calcium and normalized ionic serum calcium was lower in the case group (9,77 ± 0,68 mg/dL and 1,34 ± 0,12 mmol/L versus 10,32 ± 0,55 and 1,44 ± 0,09, p= 0,001 and 0,002 respectively). There was a tendency for PTH to be lower in cases (80,88 ± 55,70 pg/mL for the case group and 108,89 ±58,61 for the control group, p=0,085). There were no differences in glomerular filtration rate (77,24 ± 19,01 ml/min for the case group and 71,56 ± 21,56 in the control group, p=0,33). BMD was similar for both groups, although there was a tendency for the control group to be greater. Data at baseline is summarized in Table 1.

The follow-up time for the control group was 3,2 ± 1,35 years while in the case group was 2 years (p<0,001). At the end of follow-up both groups decreased their levels of both calcium and ionized calcium (-1,52% ± 5,38 and -1,81% ± 4,63 for the case group versus -8,44% ± 7,77 and -14,54% ± 9,23 for the control group), although the reduction was greater in the case group (p<0,001 and <0,0001 respectively). PTH levels increases in the case group (+61,64% ± 71,09) while decreases in the control group (-28,04% ± 74,77 p<0,0001). Data at the end of follow up is summarized in Table 2.

Both groups increased BMD in the lumbar spine (+6.51% ± 8.2 in the case group and +4.16% ± 7.01 in the control group, p=0,25), and in the distal third of the radius (+0.29% ± 7.65 in the case group and +0.25% ± 4.81 in the control group p=0,986), but the case group had decreased BMD at the femoral neck (-5.81% ± 15.32) and total (-1.03% ± 11.44), while the control group increased it (+4.04% ±7.06 for the femoral neck and +2.42% ± 5.61 for the total neck), although the difference was only statistically significant for the femoral neck (p=0.041). The parameters that compare both groups are summarized in Table 3.

47,06% of patients from the case group versus 19,64% of patients from the control group had undergone parathyroidectomy before follow-up (p=0,024). 64% of patients from the control group underwent surgery during follow-up vs. 11,76% from the case group (p=0,01). There were no differences in fractures before and after follow-up. Additionaly, the control group suffered more nephrolithiasis after follow-up (0% for the case group vs. 26,79% for the control group p=0,017). Qualitative variables are summarized in Table4.

Table 1: Biochemical data of mineral metabolism and BMD at baseline

	Case n=17		Control n=56		p value
	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	**75,71**	**6,93**	**62,90**	**11,77**	**<0,0001**
Glomerular filtration rate (mL/min)	77,24	19,01	71,56	21,56	0,334
Serum calcium(mg/dL)	**9,77**	**0,68**	**10,32**	**0,55**	**0,001**
Ionic serum calcium (mmol/L)	**1,34**	**0,12**	**1,44**	**0,09**	**0,002**
24 hour urine calcium	214	90	293	141	0,11
PTH (pg/mL)	80,88	55,70	108,89	58,61	0,085
Vitamin D (ng/mL)	**24,19**	**10,29**	**16,82**	**8,59**	**0,008**
BMD lumbar spine (g/cm^2)	0,810	0,112	0,868	0,138	0,11
BMD femoral neck (g/cm^2)	0,680	0,084	0,697	0,109	0,60
BMD total neck (g/cm^2)	0,795	0,128	0,815	0,113	0,53
BMD distal third of radious (g/cm^2)	0,562	0,080	0,601	0,100	0,283

Table 2: Biochemical data of mineral metabolism and BMD at the end of follow-up

	Case n=17		Control n=56		p value
	Mean	Standard deviation	Mean	Standard deviation	
Follow-up time	**3,2**	**1,3**	**2,0**	**0,0**	**0,001**
Glomerular filtration rate (mL/min)	73,85	21,02	76,29	23,41	0,73
Serum calcium(mg/dL)	9,61	0,73	9,43	0,58	0,30
Ionic serum calcium (mmol/L)	**1,31**	**0,11**	**1,25**	**0,08**	**0,038**
PTH (pg/mL)	**119,82**	**82,51**	**66,55**	**63,03**	**0,024**
Vitamin D (ng/mL)	24,94	6,64	22,76	12,25	0,53
BMD lumbar spine (g/cm^2)	0,860	0,115	0,900	0,138	0,281
BMD femoral neck (g/cm^2)	**0,639**	**0,099**	**0,737**	**0,111**	**0,041**
BMD total neck (g/cm^2)	0,780	0,112	0,841	0,118	0,063
BMD distal third of radious (g/cm^2)	0,547	0,078	0,600	0,101	0,126

Table 3: Change in biochemical data of mineral metabolism and BMD expressed as a percentage (%)

	Case n=17		Control n=56		p value
	Mean	Standard deviation	Mean	Standard deviation	
Glomerular filtration	-4,21	21,09	+4,9	25,24	0,22
Normalized serum calcium	**-1,52**	**5,38**	**-8,44**	**7,77**	**<0,001**
Normalized ionic serum calcium	**-1,81**	**4,63**	**-14,54**	**9,23**	**<0,0001**
PTH	**+61,64**	**71,09**	**-28,04**	**74,77**	**<0,0001**
Vitamin D	+19,53	63,98	+56,04	101,34	0,24
BMD lumbar spine	+6,51	8,20	+4,16	7,01	0,25
BMD femoral neck	**-5,81**	**15,32**	**+4,04**	**7,06**	**0,041**
BMD total neck	-1,03	11,44	+2,42	5,61	0,245
BMD distal third of radious	+0,29	7,65	+0,25	4,81	0,986

Table 4: Parathyroid surgery, medical treatment for osteoporosis, bone fractures and nephrolithiasis.

	Case n=17		Control n=56		p value
	Number	Percentage	Number	Percentage	
Undergo surgery at any moment	10	58,82%	36	64,29%	0,683
Undergo surgery before follow-up	**8**	**47,06%**	**11**	**19,64%**	**0,024**
Undergo surgery during follow-up	**2**	**11,76%**	**25**	**44,64%**	**0,014**
Medical treatment for osteoporosis before the follow-up	9	52,94%	29	51,79%	0,93
Fractures before follow-up	0	0%	2	3,63	0,425
Fractures after follow-up	0	0%	4	7,14%	0,257
Nephrolithiasis before follow-up	1	5,88%	13	23,21%	0,112
Nephrolithiasis during follow-up	**0**	**0%**	**15**	**26,79%**	**0,017**

DISCUSSION

In this study, we provide evidence that denosumab is a safe and effective treatment for osteoporosis due to PHPT. However, the matching between cases and controls has not been perfect and we must take this into account when interpreting the results.

First, the age of the cases was much higher than the controls (76 years vs. 63 p<0,0001). This fact could be attributed to different reasons.

Denosumab is safer than bisphosphonates in patients with dysphagia and renal failure, and since both pathologies are related to aging, it is expected that the group treated with denosumab will be significantly older than those treated with bisphosphonates. Another reason is that denosumab is currently a second-line treatment when bisphosphonate treatment fails or is contraindicated, explaining that the cases have had a longer follow-up, which explains why they are older.

Second, levels of normalized and ionized calcium are higher in controls than in cases at baseline. The main reason is that at baseline there were a higher percentage of patients operated on in the case group (47.06%) compared to the control group (19.64%) with a p<0,05, reflected as a higher PTH value in the control group, although not statistically significant (p=0.085). There are additional biological mechanisms that explain why this happens regardless of PTH concentration. A study done in rodents(38) shows that PTH-sensitive Na+-dependent Ca^{2+} efflux was markedly reduced in renal cells isolated from senescent rats as compared to young rats. PTH-stimulated adenylate cyclase activity was also decreased in aging, as well as a 50% decrease in PTH receptors expressed in the nephron. Another study, this time conducted in humans(39), observed that PTH levels increased with age regardless of vitamin D, calcium or glomerular filtration levels, suggesting that the cut-off point for normal PTH levels should be increased in elderly subjects. This may be because PTH is less effective at raising calcium as we age. This was also observed in another study(40) carried out in healthy men, those who were older had higher PTH levels but not serum calcium. All these arguments would explain why calcium levels but not PTH levels are higher in our control group, who are significantly younger than the case group.

Third, the follow-up time was shorter in the control group. As the control group had a tendency to gain BMD but not statistically significant, perhaps if the follow-up had been one more year, more differences between groups would have been appreciated.

By last, vitamin D levels in cases were significantly higher than in controls ($p<0,05$). This is probably due to the fact that the control group had a longer medical follow-up and, therefore, more chances of having detected a deficiency, but we have not recorded it in the database. Another reason is that calcaemia in the control group is higher than in the case group; therefore this may favor physicians to be more reluctant to prescribe vitamin D in subjects with higher serum calcium concentrations

The matching has been correct in terms of received medical treatments, fractures, nephrolithiasis and bone mineral density. At baseline, both groups had the same bone mineral density (BMD), although there was a tendency for the case group to have less BMD. This is probably because the case group was older.

At the end of the follow-up, the PTH levels in the cases increased significantly, while in the controls they decreased. This is because a much larger number of controls underwent surgery during follow-up. This also explains why calcium levels fell more in controls than in cases. In the case group, the elevation of PTH was not able to raise calcium for two reasons. On the one hand, the hypocalcaemic effect of denosumab dampens the calcium elevations due to the increase in PTH, and on the other hand, as previously stated, PTH has a lesser hypercalcaemic effect in the elderly. Although there were no differences between groups in terms of BMD, except in the femoral neck, in the group treated with denosumab there was a tendency to have less BMD. Moreover, there were no significant differences in the fractures produced between both groups. This fact supports parathyroidectomy as the treatment of choice in PHPT but also shows that denosumab could be considered as an effective option for maintaining BMD in patients with PHPT. Perhaps, if the follow-up had been longer, we would have observed an increase in the number of fractures in the case group.

There were more nephrolithiasis in the group that did not receive denosumab. This is probably not due to differences between treatments between groups, but rather to the fact that the case group is older than the control group, and as has been previously observed(41), elderly patients are less likely to develop nephrolithiasis. Otherwise, older patients are more likely to develop osteoporosis(42). In our study it does not occur because 47.06% of the cases had undergone surgery compared to 19.64% of the controls, and as previously stated, parathyroidectomy is the treatment that best prevents and treats osteoporosis related to PHPT. An additional reason is that while osteoporosis is asymptomatic and there is medical treatment for it, kidney stones are painful and there is no really effective medical treatment, therefore, it could influence both doctors and patients to be more willing to undergo surgery.

The main strength of our study is that it was carried out in a real hospital environment, therefore, its results are easily extrapolated to what happens when one or another treatment is decided according to clinical criteria. In addition, the follow-up has been long enough to observe densitometric and biochemical changes in our patients. We have had available a densitometry that evaluated the BMD changes both in the spine, as well as in the hip and the distal third of the radius at the beginning and at the end of the study.

None of our patients suffered serious adverse effects of denosumab such as osteonecrosis of the jaw or symptomatic hypocalcaemia, probably because they did not have any comorbidity that predisposed them to them and globally they are rare adverse reactions.

This is not the first study evaluating the efficacy of denosumab in the treatment of PHPT-induced osteoporosis. Daichi Miyaoka et al(43) compared 19 patients with PHPT who underwent parathyroidectomy versus 19 patients who were not candidates for surgery and received denosumab. The follow-up period was 12 months. At baseline, as in our study, the age of patients who were not candidates for surgery (71,8 ± 7,1) was significantly higher than the ones who underwent surgery (63,2 ± 10,4 with a p value=0,005). The levels of calcium were also higher in younger patients (10,2 ± 0,5 mg/dL for denosumab group and 11,5 ±1,0 in de surgery group p<0,001) , and there were no significant differences in BMD between groups. Contrary to our study, the glomerular filtration rate of the denosumab-treated group was significantly lower than of the operated group. At the end of follow-up, PTH levels decreased dramatically in the operated group (from 140pg/mL to 33.0pg/mL with a p value <0,05) but continued to increase in the denosumab-treated group (from 46,3 pg/mL to 59,4 pg/mL p<0,05). Calcium levels decreased in the operated group (from 11,5mg/dL to 9,4mg/dL with a p value<0,05) but remained stable in the group treated with denosumab despite the increase in PTH. The fact that both our study and the one presented have similar biochemical changes gives more weight to the results obtained.

However, we have had different results with regard to BMD. In our study, both groups gained similar bone density in the lumbar spine, while in the present study the operated group gained greater bone density in both the lumbar spine and the hip. This may be due to the fact that in our study 44.64% of patients in the control group underwent surgery during follow-up, compared to 11.76% in the case group, while in the cited study we are comparing a group of 100% operated patients versus a group of 0% operated patients. Therefore, as surgical intervention is the most effective treatment to treat osteoporosis secondary to PHPT, it is to be expected that if we compare a group that has a greater number of operated patients with one that has lower percentage the bone density gain for the first group would be greater. Moreover, this study just

had a follow-up of 12 months, so if the follow-up would have been as longer as our study, the results will be probably accentuated. Nevertheless, we must note that the group treated with denosumab increases its BMD instead of not being operated, underlining the effectiveness of denosumab to treat secondary osteoporosis due to PHPT.

Regarding nephrolithiasis, both our study and the one cited suffer fewer stones in patients treated with denosumab, although this probably has nothing to do with denosumab, but rather that elderly patients are less likely to develop nephrolithiasis, and because patients with renal lithiasis are more likely to assume the surgical risks.

C Eller-Vainicher et al(44) in a retrospective observational study compared a group of 65 women with osteoporosis secondary to PHPT with 25 women diagnosed with primary osteoporosis (PO) during a 24-month follow-up. Both groups were treated with denosumab. As in our study, the reason why patients with PHPT were not operated was surgical contraindication. Unlike our study, the researchers did manage to get both groups to have the same age (78,6 for the PHPT group and 78,8 for the PO group), probably because the comparison was not made between operated PHPT vs. not operated, but among women with PHPT and PO. The patients in this study had forms of PHPT that were more severe than ours(serum PTH concentration 88,88 ± 55,7 in our study vs. 117,5 ± 42,3 in the cited study), probably because in our study there was already a notable percentage of those operated on, while in the present there is none. Interestly, both groups had the lowest bone denisty located at the femoral neck at baseline. This may explain why our case group lost bone density only in the femoral neck, since it may be due to aging and not so much to treatment with denosumab, since it is well known that BMD increases in this location in patients with PO treated with denosumab(45). At the end of the follow-up, the biochemical changes were very similar to those obtained in our study. PTH levels continued to increase, but calcium decreased slightly, providing further evidence of the hypocalcaemic effect of denosumab. At the end of follow-up, both groups had increased BMD at both the lumbar spine and the hip, but surprisingly the PHPT group increased their BMD significantly more compared to the PO group. The data suggest that, in older women with PHPT, 24 months of denosumab therapy increases BMD higher than it does in matched older women with PO.

So our findings regarding BMD and bone fractures in patients with PHPT are in accordance to a couple of previous studies.

The main strength of our study is that the data has been obtained from real life, while the main limitations are the small sample, the differences between cases and controls at baseline and the retrospective study design. Finally, the various

treatments studied were not prescribed to find differences between them, but according to individualized medical reasons.

CONCLUSION

Denosumab seems a reasonably safe and effective therapeutic option for preserving BMD and preventing bone fractures in patients with hyperparathyroidism undergoing parathyroidectomy or not.

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