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Prevalence of hypovitaminosis D and secondary hyperparathyroidism in the Spinal Cord Injury Unit in Gran Canaria. Preliminary study

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Summary
Background: vitamin D deficiency is very common, and has been demonstrated in multiple studies in both the general population and in patients with different pathologies. However, it has been little studied in patients affected by spinal injury.
Objective: to study the prevalence of hypovitaminosis D and the possible development of secondary hyperparathyroidism in a population of patients with spinal injury.
Material and method: transverse descriptive study carried out in 104 patients affected by spinal injury. A clinical history was taken, a detailed physical examination carried out and a blood sample while fasting taken, with the least possible compression, from all patients. The analytical parameters were analysed using automated techniques and the determination of 25-hydroxyvitamin D (25HCC) and parathyroid hormone (PTH) was performed using electroimmunochemiluminescence (ECLIA).
Results: the global mean value of 25-hydroxyvitamin D was 20.1 ± 11.6 n/ml. 84.6% of the patients had blood values of 25-hydroxyvitamin D lower than 30 ng/ml and 62% of all patients showed values lower than 20 ng/ml. The prevalence of vitamin D deficiency was similar in men and women. However, although we found an inverse correlation between levels of PTH and hydroxyvitamin D, only 5.8% of patients ended up developing secondary hyperparathyroidism.
Conclusions: there is a high prevalence of hypovitaminosis D in patients with spinal injury. It is advisable, therefore, to include a study of this metabolite in the care protocol of these patients to correct these deficiencies as and when they are found.

Key words: *vitamin D, parathormone, spinal injury.*

Introduction

Vitamin D plays an important role in bone mineral metabolism since it is involved in the regulation of levels of calcium and phosphorus, and its deficiency may be an epipathogenic factor in osteoporosis. However, in the last few years there has been clear evidence which gives the action of vitamin D highly important effects outside the bone, which fundamentally alters musculo-skeletal function. Recent studies have reported that vitamin D acts on the immune system, prevents pathologies such as arteriosclerosis[1], arterial hypertension[2], resistance to insulin[3] and hyperglycemia[4], in addition to being related to the prevention of various types of cancer[5-7].

Blood levels of vitamin D are a significant risk factor in the diminution of bone mass and in the increased risk of fractures in these patients. Some studies have been published which show deficient levels of vitamin D in patients with spinal injury, the prevalence of this deficit being estimated at between 30 and 32%[8,9].

The measure of blood levels of 25-hydroxyvitamin D (25HCC) is the universally accepted form of indicator for vitamin D reserves[10]. There is not a unanimous consensus regarding the blood levels of 25-hydroxyvitamin D sufficient to ensure bone health in the general population, and even less in patients with spinal injury. However, it tends to be accepted that ideally these levels should be, as a minimum, 30 ng/ml[11].

Patients with spinal injury usually have osteoporosis secondary to immobilisation and fractures, above all in the lower limbs. The additional role which vitamin D deficiency may have in its etiopathology has not been determined. Therefore, we carried out this study in a population of patients with controlled spinal injury in the Spinal Injury Unit of the Island University Hospital Complex for Mothers and Children in Gran Canaria.

Patients and methods

This is a transverse observational study carried out in 104 patients who were admitted to the Spinal Injury Unit of the Island University Hospital and who were seen either at a first visit or at a review, during the year 2012. A required criterion for inclusion in the study was the existence of an irreversible spinal injury. The patients were informed of the objectives of the study, and had previously signed their informed consent to participate. The study was approved by the Committee for Ethics and Clinical Trials of the Island University Hospital.

In all cases we applied the clinical protocol for the study and follow up of patients with spinal injury, which included clinical history, physical examination, biochemical parameters (haemoglobin, glucose, urea, creatinine, calcium, phosphorus, total proteins, lipid profile, tartrate-resistant acid phosphatase (TRAP), PTH, 25-hydroxyvitamin D, beta-crosslaps, osteocalcin and amino-terminal peptide of collagen type 1 - P1PT).

Blood was taken in fasting, with the least possible compression and the general biochemical parameters (haemoglobin, glucose, urea, creatinine, calcium, phosphorus, total proteins, lipid profile) were measured with an autoanalyser; the TRAP by spectrophotometry; and the PTH, 25HCC, beta-crosslaps, osteocalcin and P1NP by electroimmunochemiluminescence (EIQL). The period of collecting the samples extended from March to May 2012.

Normal levels of vitamin D were considered to be where blood values of 25-HCC above 30 ng/ml; insufficiency, those between 20-30 ng/ml; and deficiency, figures below 20 ng/ml, in accordance with the position document of the International Osteoporosis Foundation (IOF)[12]. With respect to PTH, normal values are considered to be <88 ng/ml, as set by the laboratory, and levels higher than this are indicative of secondary hyperparathyroidism.

A descriptive statistical analysis of the study's baseline data was carried out. For this, we calculated the absolute and relative frequencies in the case of the qualitative variables. The quantitative variables were summarised by means of mean ± standard deviation or percentiles with average interquartile range, respectively, depending on whether or not there is a normal distribution after being subject to the Kolmogorov-Smirnov test.

Results

In table 1 we show the characteristics of the population studied. The 104 patients with spinal injury had an average age of 43.4 years, and 74% were men. 86.5% of the patients had had an injury of traumatic origin. 40% were tetraplegic. The average time from the injury occurring to the date of the study was 8 years.

Table 2 shows various analytical value data, such as renal function and lipids (total cholesterol, triglycerides and HDL-cholesterol). The average values of these parameters were within normal values.

In table 3 we show the analytical data related with bone metabolism. The median values of 25-HCC were globally 20.1 ± 11.6 ng/ml, being 20.1 ± 11 ng/ml in men and 19.9 ± 13.5 ng/ml in women (p=0.919). According to established parameters for normality, 84.6% of those with spinal injury had blood values of 25-hydroxyvitamin D lower than 30 ng/ml, and 62.5% had values lower than 20 ng/ml. The prevalence of vitamin D deficiency was similar in both sexes (Table 4).

The analysis as a function of age, with the limit established at 50 years of age, showed that the patients younger than 50 had a higher percentage of vitamin D deficit (66.6%) than those over 50 years of age (53.1%). However, among those over 50 there was a higher percentage of patients in the insufficient range for vitamin D (37.5%).

When we carried out the comparison of the values of 25HCC as a function of the level of spinal injury, we observed that the paraplegic patients had values of vitamin D indicative of vita-

min D deficit higher than the tetraplegics (69% vs 61.2% respectively).

In terms of the other parameter studied, the PTH, a prevalence of secondary hyperparathyroidism of 5.8% was found. We obtained a statistically significant inverse correlation between levels of PTH and those of 25HCC (r= -0.262; p= 0.007) (Figure 1).

Discussion

Patients with chronic spinal injury had a higher prevalence of fragility fractures, above all in the long bones, due essentially to the reduction in mobility, although there may be other mechanisms which contribute, such as hypovitaminosis D.

In fact, some studies carried out earlier describe the existence of hypovitaminosis D in patients affected by spinal injury. Thus, in a group of 100 military personnel with this pathology studied in a the Veterans Hospital in New York, Baumann et al. found a deficiency in vitamin D in 32% of patients affected both by paraplegia and tetraplegia. These were patients of both sexes, with an average age of 51 years and an average of 20 years since the acute spinal injury. The threshold chosen by the authors for the establishment of deficiency was 16 ng/ml, a value much lower than the currently recommended value of 30 ng/ml, which means that in applying the same cut off point, the prevalence of vitamin D insufficiency would be even higher. Similarly, Hummel et al., in 62 patients of both sexes with spinal injury, found hypovitaminosis D in 39% of cases[8], establishing the deficiency threshold at 75 nmol/L of 25HCC (equivalent to 30 ng/ml) which is precisely the figure currently accepted for the establishment of vitamin D insufficiently[13].

In our study we have applied this cut off point, 30 ng/ml of 25-hydroxyvitamin D, which establishes vitamin D insufficiency as those values of 25-hydroxyvitamin D lower than 30 ng/ml, and deficiency to those lower than 20 ng/ml. These cut off points have been suggested by various authors[14-17] and by the IOF in their position document[12]. On the basis of this, in Spain a high prevalence of hypovitaminosis D has been reported both in the general population and in older people[18,19], and more specifically, in various pathologies[20-22].

It is known that low levels of vitamin D favour the development of secondary hyperparathyroidism[13,18]. In our patients we found a negative or inverse correlation between levels of PTH and those of 25-hydroxyvitamin D, which although statistically significant, we consider to be weak (r=0.262). Not all patients with low levels of vitamin D had secondary hyperparathyroidism, which suggests that there are other factors which may affect its presentation.

The patients had normal renal function, estimated by the determination of blood creatinine and urea, and blood levels of TSH were also within normal levels.

Table 1. Baseline characteristics of the population studied

Variable	Value	Percentage (%)
Number	104	100
Men	77	74
Women	27	26
Cause of spinal injury		
Traumatic	90	86.5
No traumatic	14	13.5
Level of spinal injury		
Quadriplegia	41	39.4
Paraplegia	63	60.6
Functional status (Scale Asia)		
1 (Complete injury)	56	53.8
2 (Incomplete injury)	48	46.2

Table 2 Biochemical data for renal and thyroid functions and lipids (Mean ± typical deviation)

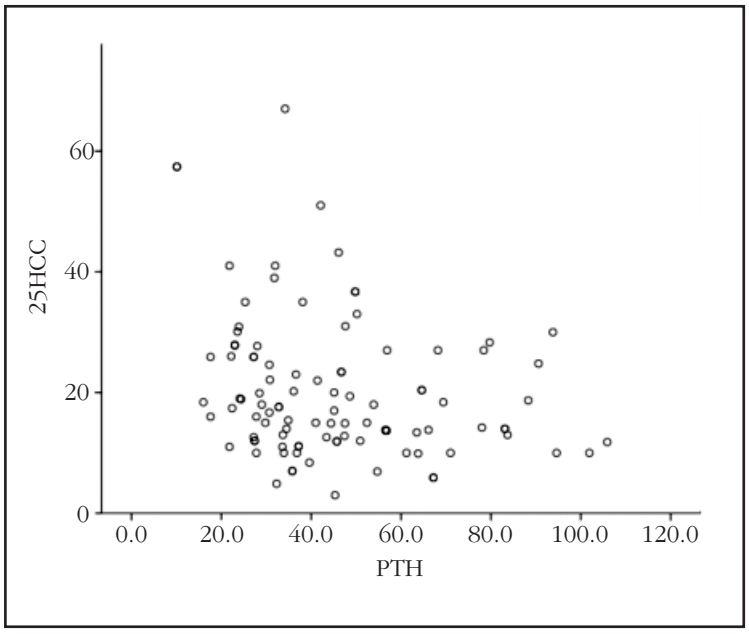
Variable (Units)	Value obtained	Values reference
TSH (UI/l)	1.8 ± 1.1	0.5 - 5
Urea (mg/dl)	29.2 ± 8.8	15 - 45
Creatinine	0.8 ± 0.2	0.8 - 1.4
Cholesterol (mg/dl)	191.1 ± 44.1	120 - 220
Triglycerides (mg/dl)	178.8 ± 9.5	30 - 200
HDL-Cholesterol (mg/dl)	47.1 ± 21.5	35 - 65

Table 3. Biochemical data related to bone mineral metabolism (Mean ± typical deviation)

Variable (Units)	Value obtained	Values reference
Calcium (mg/dl)	9.6 ± 0.4	8.8 - 10.4
Phosphorus (mg/dl)	3.3 ± 0.5	3.3 - 5
Total protein (g/l)	7.1 ± 0.4	6.2 - 8
Corrected calcium (mg/dl)	9.7 ± 0.4	8.8 - 10.4
Osteocalcin (ng/ml)	20.2 ± 9	14 - 46
TRAP (UI/l)	2.3 ± 0.6	0.1 - 3.9
Beta-crosslaps (ng/ml)	0.3 ± 0.2	0 - 0.5
P1NP (ng/ml)	43.3 ± 23.7	<36.4
PTH (pg/ml)	45.2 ± 21.1	15 - 88
25-HCC (ng/ml)	20.1 ± 11.6	>30

TRAP: tartrate-resistant acid phosphatase; P1PT: amino-terminal peptide of collagen type 1; PTH: parathormone; 25HCC: 25-hydroxyvitamin D.

Figure 1. Correlation between blood levels of 25-hyrdroxyvitamin D and PTH in patients with spinal injury.
(R= - 0,262; p=0,007)



The markers for remodelling were within the limits established as normal by our laboratory and which are shown in table 3. An increase in markers for resorption might have been expected, given that an increase in the destruction of bone in a state of immobility has been reported in both humans and animals[23-25], but we did not find this. It is possible that this was due to the long period of time since the spinal injury had occurred, since the increase in resorption and the loss of bone mass occurs in the first few weeks after the injury[26].

One of the limitations of our study is our having determined the 25HCC using IQL. It is well known that the standard reference model for the measurement of vitamin D is high pressure liquid chromatography (HPLC)[27], to which we did not have access in our Unit. Another limitation is that of having carried out only a descriptive study without using a control group with which to compare the results, but it should be taken into account that the levels set for the establishment of insufficiency and deficiency are already, practically speaking, a matter of consensus (30 ng/ml and 20 ng/ml of 25HCC, respectively)[11-15,17,20] as well as the upper limit of PTH, which has been established as normal at 88 ng/ml in our laboratory through other studies[28-31]. On the other hand, one of the strengths of the study is its sample size, 104 patients with spinal injury, the highest number found in the literature which we have been able to consult on this matter.

In conclusion, a high proportion of patients with chronic spinal injury had blood levels of 25-hydroxyvitamin D which may be considered as "insufficient", which is why we believe that it is necessary to generalise the study of vitamin D levels in these patients in order to detect and correct deficiencies when they are seen. We should also pose the question as to whether vitamin D supplements really reduce the risk of osteoporosis and fracture, which may be the objective of other studies.

Bibliography

1. Chua GT, Chan YC, Cheng SW. Vitamin D status and peripheral arterial disease: evidence so far. Vasc Health Risk Manag 2011;7:671-5.

2. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 2001;86:1633-7.

Table 4. Prevalence of normality, insufficiency and deficiency of vitamin D in patients with spinal injury as a function of sex

		Normal (>30 ng/ml)	Insufficiency (20-30 ng/ml)	Deficiency (<20 ng/ml)	Total
Men	% of the total	4	6	17	27
	number	3.8	26.1	26.2	26
Women	% of the total	12	17	48	77
	number	11.5	16.3	46.2	74
Total	% of the total	16	23	65	104
	number	15.4	22.1	62.5	100

3. Boucher BJ, John WG, Noonan K. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004;80:1666.
4. Jódar-Gimeno E, Muñoz-Torres M. Vitamin D hormone system and diabetes mellitus: lessons from selective activators of vitamin D receptor and diabetes mellitus. Endocrinol Nutr 2013;60:87-95.
5. Cheung FS, Lovicu FJ, Reichardt JK. Current progress in using vitamin D and its analogs for cancer prevention and treatment. Expert Rev Anticancer Ther 2012;12:811-37.
6. Cutolo M. The challenges of using vitamin D in cancer prevention and prognosis. Isr Med Assoc J 2012;14:637-9.
7. Krishnan AV, Trump DL, Johnson CS, Feldman D. The role of vitamin D in cancer prevention and treatment. Rheum Dis Clin North Am 2012;38:161-78.
8. Hummel K, Craven BC, Giangregorio L. Serum 25(OH)D, PTH and correlates of suboptimal 25(OH)D levels in persons with chronic spinal cord injury. Spinal Cord 2012;50:812-6.
9. Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. Metabolism 1995;44:1612-6.
10. Scharla S. Diagnosis of disorders of vitamin D-metabolism and osteomalacia. Clin Lab 2008;54:451-9.
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
12. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010;21:1151-4.
13. Gómez Alonso C, Naves Díaz M, Rodríguez García M, Fernández Martín JL, Cannata Andía JB. Revisión del concepto de "suficiencia e insuficiencia" de vitamina D. Nefrología 2003;23 Suppl 2:73-7.
14. Heaney RP. Optimal vitamin D status. J Bone Miner Res 2009;24:755.
15. Holick MF. Optimal vitamin D status for the prevention and treatment of osteoporosis. Drugs Aging 2007;24:1017-29.
16. Vieth R. What is the optimal vitamin D status for health? Prog Biophys Mol Biol 2006;92:26-32.
17. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713-6.
18. Quesada JM, Coopmans W, Ruiz B, Aljama P, Jans I, Bouillon R. Influence of vitamin D on parathyroid function in the elderly. J Clin Endocrinol Metab 1992;75:494-501.
19. Quesada JM, Jans I, Benito P, Jiménez JA, Bouillon R. Vitamin D status of elderly people in Spain. Age Ageing 1989;18:392-7.
20. González-Molero I, Morcillo S, Valdés S, Pérez-Valero V, Botas P, Delgado E, et al. Vitamin D deficiency in Spain: a population-based cohort study. Eur J Clin Nutr 2011;65:321-8.
21. López-Robles C, Ríos-Fernández R, Callejas-Rubio JL, Ortego-Centeno N. Vitamin D deficiency in a cohort of patients with systemic lupus erythematous from the South of Spain. Lupus 2011;20:330-1.
22. Ríos Fernández R, Fernández Roldán C, Callejas Rubio JL, Ortego Centeno N. Vitamin D deficiency in a cohort of patients with systemic scleroderma from the south of Spain. J Rheumatol 2010;37:1355.
23. Gaudio A, Pennisi P, Bratengeier C, Torrisi V, Lindner B, Mangiafico RA, et al. Increased sclerostin serum levels associated with bone formation and resorption markers in patients with immobilization-induced bone loss. J Clin Endocrinol Metab 2010;95:2248-53.
24. Wang PL, Meyer MM, Orloff SL, Anderson S. Bone resorption and "relative" immobilization hypercalcemia with prolonged continuous renal replacement therapy and citrate anticoagulation. Am J Kidney Dis 2004;44:1110-4.
25. Yeh JK, Liu CC, Aloia JF. Effects of exercise and immobilization on bone formation and resorption in young rats. Am J Physiol 1993;264(2 Pt 1):E182-9.
26. Kim CS, Maekawa Y, Fujita M, Sato N, Nishimuta M, Ishizaki Y, et al. Immobilization on the day 14th does not disrupts the basic diurnal rhythm of bone resorption. J Gravit Physiol 2000;7:P125-6.
27. Luque de Castro MD, Fernández-Romero JM, Ortiz-Boyer F, Quesada JM. Determination of vitamin D3 metabolites: state-of-the-art and trends. J Pharm Biomed Anal 1999;20:1-17.
28. Sosa M, Jódar E, Arbelo E, Domínguez C, Saavedra P, Torres A, et al. Bone mass, bone turnover, vitamin D, and estrogen receptor gene polymorphisms in male to female transsexuals: effects of estrogenic treatment on bone metabolism of the male. J Clin Densitom 2003;6:297-304.
29. Sosa M, Jódar E, Saavedra P, Navarro MC, Gómez de Tejada MJ, Martín A, et al. Postmenopausal Canarian women receiving oral glucocorticoids have an increased prevalence of vertebral fractures and low values of bone mineral density measured by quantitative computer tomography and dual X-ray absorptiometry, without significant changes in parathyroid hormone. Eur J Intern Med 2008;19:51-6.
30. Del Carmen Navarro M, Saavedra P, Jódar E, de Tejada MJ, Mirallave A, Sosa M. Osteoporosis and metabolic

syndrome according to socio-economic status; contribution of PTH, Vitamin D and body weight: The Canarian Osteoporosis Poverty Study (COPS). Clin Endocrinol 2013;78:681-6.
31. González-Padilla E, Soria López A, González-Rodríguez E, García-Santana S, Mirallave-Pescador A, Groba Marco M del V, et al. Elevada prevalencia de hipovitaminosis D en estudiantes de Medicina en Gran Canaria, Islas Canarias (España). Endocrinol Nutr 2011;58:267-73.