Vitamin D levels in unhealed fractures

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Abstract

Introduction: Fracture lack of healing is, in general, a multi-factorial event. The aim of this study is to estimate the reference levels of Vitamin D (25OHD3) in fractures that have not healed and their association with patients' age and fracture location.

Materials and methods: Descriptive, observational and prospective study in 29 patients with unhealed fractures. We performed an estimation of seric concentration of Vitamin D (25OHD3) together with pre-operative studies. We used generalized models to estimate the effects of patients' age and fracture location, and also detect patients groups with levels lower than recommended.

Results: Sixty-eight dot nine percent of the patients had average seric concentration of Vitamin D lower than normal levels (30.0ng/ml), which were reversely associated with age, 40 years old being the cut-off point as from which other characteristics such as fracture location (in lower limbs) condition jointly fracture healing.

Conclusions: Most patients whose fracture did not heal had Vitamin D deficit, and this trait is remarkable in >40-year-old patients. It is essential to identify the patients at higher risk of lacking in Vitamin D in the first stages of the fracture treatment, since this micronutrient supplement is an acknowledged factor to decrease the risk of non-union.

Key words: Vitamin D; fracture lack of healing; non-union; Vitamin D deficit

Level of evidence: IV

Valores de vitamina D en fracturas no consolidadas

Resumen

Introducción: La falta de consolidación de una fractura es, en general, un fenómeno multifactorial. El objetivo de este estudio fue estimar los valores de referencia de vitamina D (25OHD3) en fracturas que no consolidaron, estudiar su asociación con la edad y su localización.

Materiales y Métodos: Estudio prospectivo, de observación y descriptivo en 29 pacientes con fracturas no consolidadas. Se determinaron las concentraciones séricas de vitamina D (25OHD3) junto con los estudios prequirúrgicos. Se calcularon modelos generalizados para estimar los efectos de la edad y la localización, y detectar grupos de pacientes con niveles inferiores al valor recomendado.

Resultados: El 68,9% de los pacientes tenía concentraciones séricas promedio de vitamina D inferiores al valor normal (30,0 ng/ml), que se asociaron inversamente con la edad, 40 años fue el punto de corte a partir del cual otras características, como la localización de la fractura (en huesos que afectan a los miembros inferiores), condicionan conjuntamente la falta de consolidación.

Conflict of interests: The authors have reported none.

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Conclusiones: La mayoría de los pacientes cuya fractura no consolidó tenía deficiencia de vitamina D y este fenómeno es marcado a partir de los 40 años de edad. Es importante identificar a los pacientes con mayor riesgo de presentar este déficit en las primeras etapas del tratamiento de las fracturas, ya que el aporte de este micronutriente es un factor reconocido para disminuir el riesgo de falta de consolidación.

Palabras clave: Vitamina D; falta de consolidación; seudoartrosis; déficit de vitamina D.
Nivel de Evidencia: IV

Introduction

In different studies it is reported that 5-10% of patients that suffer a fracture have some problems with bone healing.[1-3] To achieve fracture healing it is necessary to give an appropriate balance between mechanic and biological factors (locally and systemically). In some cases, why a fracture does not heal is clear—bone instability, inadequate vascularization or poor contact between bone fragments, all of which can hamper fracture healing.[4] Nevertheless, in some patients fractures with adequate stabilization and surrounded by optimal conditions do not heal. Multifactor interactions or systemic personal predisposing factors could explain this event. Metabolic responses to the fracture involve endocrinal factors, biochemical interactions between growth factors, bone morphogenetic proteins, vitamins, minerals and hormones. Decline in any of these factors could affect fracture healing. Many endocrinal and metabolic conditions that have influence on these factors are associated with disorders in bone metabolism.[3-13]. Vitamin D acts on bone metabolism and Vitamin D deficit could have influence on progression of the fracture to lack of healing. Vitamin D is a fat-soluble vitamin that acts as a hormone; it favors bone quantity and quality, decreasing bone re-absorption induced by parathyroid hormone and cytokines, boosting formation of cortical bone, decreasing cortical porosity, and increasing the number and function of osteoblasts by inducing bone growth factors and synthesis of proteins in the bone matrix. Moreover, it increases bone resistance and promotes reparation of micro-fractures, because it sustains vitality and function of osteocytes.[14]

Vitamin D deficit has been reported in different races and age groups—even young and healthy cohorts have been found to lack Vitamin D.[14-18.] Vitamin D deficit, defined as low circulating concentrations of hydroxyvitamin D (25OHD) is worldwide distributed and represents a public health issue.[17] Classifications of Vitamin D nutritious status have varied over the past few years; many experts affirm that 25OHD 30 ng/ml are optimal concentrations for both Vitamin D classic actions on mineral metabolism and its non-classic actions on health in general.[18] Prevalence of Vitamin D deficit is high among patients with fragility fractures, females, elderly people, and bed-confined and institutionalized people.

The objective of this study was to analyze and outline, on the basis of age and other characteristics, Vitamin D plasmatic concentrations in patients with unhealed fractures who were given appropriate stabilization techniques and showed adequate local factors and fracture setting. We set out the following hypothesis—seric concentrations of Vitamin D are low in these cases, and these findings are associated with patients' age, all of which could represent the underlying causes of lack of healing in these fractures.

Materials and methods

We carried out an observational, prospective, descriptive study which included 35 patients with unhealed fractures, assessed between 2012 and 2014. Inclusion criteria were both sex patients, skeletal maturity, and open or closed fractures that did not heal despite appropriate —surgical or conservative—stabilization techniques and good local biology. Fractures were considered not to have healed when they did not heal in the expected time specific for every bone location. Patients with bad stabilization (poor mechanic stability, lack of contact between fracture bone ends), poor biology in the fracture site (loss or decay of soft tissues coverage), infection, renal failure, considerable generalized osteoporosis, long-term glucocorticoid treatment, biphosphonates treatment, diabetes, smoking and any abnormality in the phospho-calcium metabolism were excluded. Six patients were excluded during the study (four of them because of infected non-union, and two because of biphosphonates treatment). The final sample included 29 patients (26 males and 3 females) aged, on average, 38.2 years old (+/-15.25 years) whose weight and height were recorded in all cases. Average time from fracture to sampling was 12.62 months, and the sites of fracture lack of healing were: femur (9 cases), humerus (5 cases), tibia (5 cases), scaphoid (5 cases), ulna, (two cases), radius (2 cases), and clavicle (one case). The non-union type was determined on the basis of the Weber's classification: oligotrophic, atrophic and hypertrophic.21 Types of non-union were 52% oligotrophic (15 cases), 21% atrophic (6 cases) and 28% hypertrophic (8 cases). Lack of healing was always confirmed on the basis of one or more of the following findings: 1) movement at the level of the fracture site during physical examination; 2) movement at the level of the injury when applying stress maneuvers under fluoroscopy; and 3) lack of bone bridges in 0 to 4 bone cortexes in anterior-posterior and lateral X-rays, and in the different CT scan sections.

Once bone non-union had been identified and before performing surgery for fracture setting and osteosynthesis, patients' Vitamin D (25OHD3) seric concentrations were assessed together with the pre-operative studies. To estimate plasmatic concentrations we used the method of chemoluminescence.[22] As reference level (normal level) we adopted ≥30.0 ng/ml on average.

So as to outline Vitamin D behavior on the basis of patients' specific variables, such as age, weight —both on continuous scales— surgery location (qualitative), number of previous surgeries, among others, fracture location was classified as affecting lower or upper limbs. Thus, surgeries in scaphoid, humerus, ulna and radius were included in one group, whereas surgery in tibia and femur were included in another one.

On the other hand, after describing joint distribution of Vitamin D concentrations and age, and assessing the relationship between both variables, we established a cut-off point in 40 years old and evaluated the effect of co-variables within each group of patients (< 40 and > 40 years old).

Given asymmetry in Vitamin D distribution (Figure 1), we estimated generalized models (Rabe-Hesketh & Skrondal, 2008) with Gamma response, Identity link function and systematic component, including, in the first stage, co-variables at their original scale (multiple regression models) and then classified co-variables (factorial structure models). Hypothesis tests with respect to the level 30 ng/ml were also carried out assuming the previous distribution. All tests were conducted using the Stata 14.0 program (Statacorp LP. College Station, TX, USA, 2015).

Results

In Figure 1 there is a detail of the distribution of frequencies of Vitamin D in the assessed population; it shows an asymmetric pattern not centered on the adopted reference level.

Six patients received early orthopedic treatment (20.6%); the rest of them had been operated on; among them, 45% had a previous surgery; 27.5%, two previous surgeries, and 6.8%, four previous surgeries. There was no difference in the prevalence of types of fracture lack of healing between the groups (p= 0.733); average time between fracture and surgery plus assessment of Vitamin D was 15.9 +/- 16 months (ranging from 2 to 79) and in the sub-group with Vitamin D deficit, these values averaged 13.9 +/- 12.10 months (p= 0.442).

Estimations made in this model are shown in Table 1. Part I shows estimations of the co-variables global effect —age, weight and location of the surgery (in two groups)—; only age had significant negative effects. Results show that, in absolute terms, as age increases, average levels of Vitamin D decrease. When the number of previous surgeries was incorporated in the model, effects were not significant (p= 0.39).

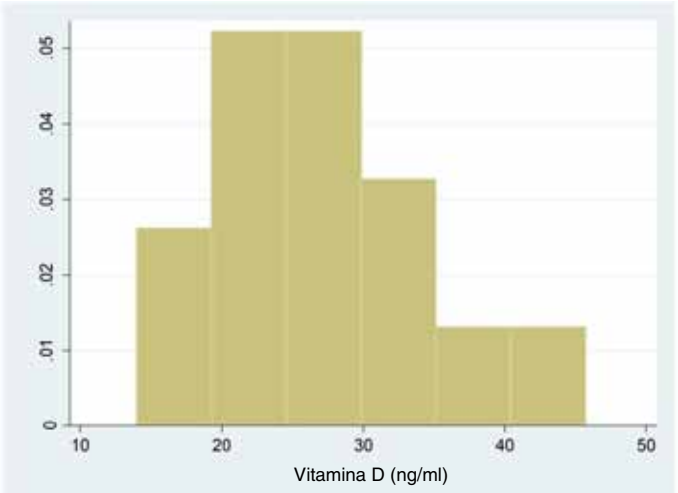

Figure 1. Distribucion of frequencies of Vitamin D among the assessed patients

In figure 2, relationship between Vitamin D levels and age is detailed. Response levels show to be stable (p= 0.163, Table 1, part II) until approximately 40 years old; as from that age, the lineal association between both variables becomes reverse (negative lineal relationship, p<0.001). Table 1 (parts II and III) shows the estimated levels for lineal coefficients in each age group; this way, in >40 years old patients, average Vitamin D decreases approximately 0.32 ng/ml every year.

Table 1. Estimated levels and standard errors (SE) of co-variable effects

I. Co-variables	Coefficient	SE	P
Age (years)	-0.294	0.077	<0.001**
Weight (kg)	-0.110	0.079	0.166
Fracture location			
1 vs. 0	2.253	2.421	0.352
II. <40 years old patients			
Age (years)	0.361	0.259	0.163
Weight (kg)	-0.203	0.098	0.040*
Fracture location			
1 vs. O	-0.917	3.600	0.864
III.>40 years old patients			
Age (years)	-0.319	0.081	<0.001**
Weight (kg)	0.034	0.080	0.669
Fracture location			
1 vs. 0	5.754	2.361	0.015*

**Highly significant, *significant a = 0.05.
†Grouped in two: 0 (tibia/femur), 1 (scaphoid/humerus/ulna/radius).
Reference (*baseline*): Group 0.

So as to understand the effects of the assessed factors, we analyzed their interactions in the changes of Vitamin D levels. Results are shown in Table 2. In absolute terms, Vitamin D average levels did not change (p= 0.976) in the two groups based on surgery location (27.3 +/- 7.4 and 27.4 +/- 8.6 ng/ml in groups 0 and 1 respectively), although Vitamin D average levels did change in age groups— 30.00 +/- 1.74 (<40 years old) and 22.28 +/- 1.86 (>40 years old, p= 0.0094). Therefore, given the distinctive signs of association between Vitamin D levels and age shown in Vitamin D average levels, these average levels changed significantly (p= 0.015) when age was incorporated in the classification of the patients (Table 2).

To illustrate the tendencies of Vitamin D and age in the context of fracture location, Figure 3 shows the dispersion diagrams for every group. There is a strong inverse association between response and age, especially in Group 0 (fracture lack of healing with surgical treatment in the upper limbs in >40 years old patients). In the supplementary group, both levels are similar.

These results give objective elements to assess the dependence and the relationship between Vitamin D levels and age, and surgery location in patients with unhealed fractures. Regarding the recommended Vitamin D levels, the sample of the assessed patients had an average of 27.34 ng/ml [CI95% 24.34-30.34], with no differences from the 30 ng/ml reference levels (p=0.08). Nevertheless, at the time of grouping by age, >40 years old patients showed levels significantly lower than that reference (p=0.0012) (Table 2). Finally, it is worth mentioning that 29 ng/ml was the 70 percentile estimated level of response distribution (Vitamin D).

Table 2. Vitamin D average levels and standard deviations (ng/ml) in patients grouped on the basis of age and location of the unhealed surgery

Age Location	<40 years old	>40 years old
Group 0: scaphoid, humerus, ulna, radius	31.07 ± 5.39	19.76 ± 4.42
Group I: femur, tibia	28.81 ± 9.69	24.80 ± 6.51
Average value (ng/ml)	30.00	22.28
95% Confidence Interval	[26.34-33.66]	[18.07-26.49]

Discussion

Vitamin D plays a key role in calcium homeostasis, and in the development and maintenance of bone metabolism.[23] There are multiple studies that assess the importance of Vitamin D for bone, but few of them relate Vitamin D to the metabolism of the fracture bone callous. Already in 1971, Del Sel considered the importance of elucidate "what are the bone conditions that, because of their unknown etiology and their characteristics must be considered metabolic mistakes, or, in other words, which ones of them are worth considering their more likely chemical background.

Bone physical changes with a radiologic, anatomic and histological parallel, also show in chemical modifications and, in the same way, primitive chemical disorders have

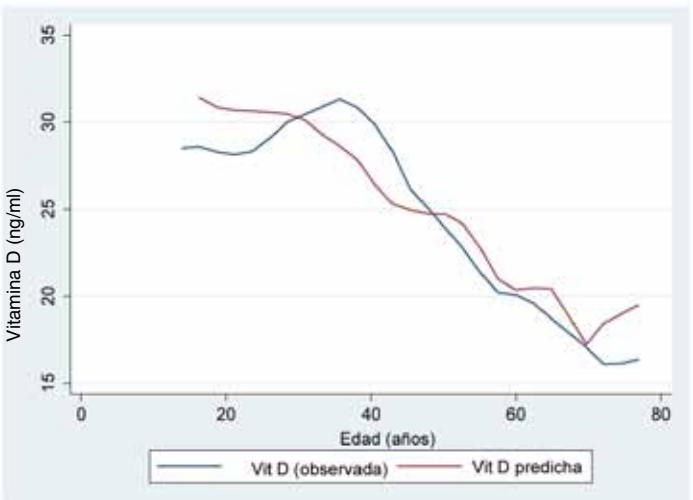

Figure 2. Verified and predicted Vitamin D levels as stated by the Gamma generalized model vs. patients' age.

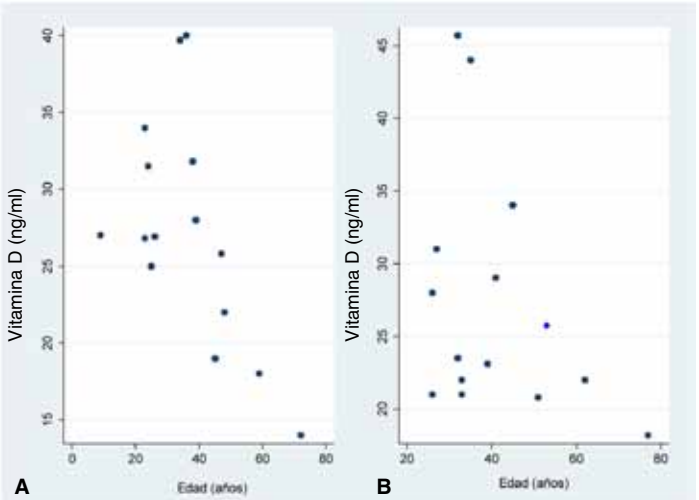

Figura 3. Dispersion diagrams between Vitamin D and age, by unhealed surgery location group: A, Group 0 and B, Group 1

influence on physical and morphologic aspects, what creates a vicious circle whose departing point sometimes is difficult to spot".[24]

The main limitations of this work are: evaluation of fracture lack of healing in long and short bones, treated conservatively and surgically, what could alter final outcomes; the size of the sample and the lack of a control group (healed fractures).

The role that metabolic bone conditions and endocrinal disorders play in non-union is not widely addressed in bibliography. Lancourt and Hochbert reported results that lead to affirm that hyperparathyroidsm is a causal factor in non-union.[25] Brinker et al. assessed a patients sample with endocrinal and metabolic disorders and lack of union, and showed that a great proportion lacked in Vitamin D with low urinary calcium concentrations and thyroid hormone; in this study, 21 of the 37 patients had 25OH sub-type Vitamin D deficit; three of them also had 1.25OH.26 subtype Vitamin D deficit.

Avenell et al., in a systematic revision and the meta-analysis of a group of > 65 years old males and females, with senile or post-menopause osteoporosis, found a decrease statistically significant in the risk of hip fracture in the patients treated with Vitamin D and calcium versus placebo or not treatment at all.[27] Other study shows that seven-year follow-up in >60 years old females with calcium and Vitamin D supplements decreases new fractures incidence in 29%.[28] Pourfeizi et al. assessed 62 <50 years old patients with tibial closed simple diaphyseal fracture treated with intramedullary naling. They had neither local nor systemic risk factors. After a 7.5-month follow-up, 30 fractures had not healed. Prevalence of Vitamin D deficit in these patients was of 60% compared to 30% in those patients with adequate fracture healing.[29]

We found a statistically significant correlation between the increase in age and Vitamin D deficit (Table 1), that can be compared to that of other studies. In Europe, prevalence of Vitamin D deficit among the elderly varies between 40 and 90%, what may be related to the regional characteristics of the diet.[30,31] In Argentina, 65-year-old healthy adult outpatients in the northern, central and southern areas of the country had percentages of 25OHD deficits (<20ng/ml) of 52%, 64% and 87%, respectively; and inadequate levels (<30 ng/ml) of 82%, 90% and 98%, respectively.[32] In Ciudad Autónoma de Buenos Aires, those with less 25OHD concentrations were the less affluent, with lower intake of food rich in Vitamin D and with lower exposure to the sun.[33]

The relationship between the decrease in Vitamin D levels and weight gain in the <40 year-old ones also showed significant differences (Table 1). This coincides with data published by other studies.[14,34] Wortsman et al. compared subjects with >30 BMI with others whose BMI was <25. With one exposure to UV (UV-B) rays, 25OHD concentration increased in both groups 24 hours later, but in the obese, the increase was worth half what had been in the control group.[35]

In spite of the incidence of Vitamin D deficit, the American Society of Endocrinology states that there is no evidence that justifies a systematic massive study of the population to find this vitamin deficit; on the contrary, this should be studied in the risk groups (Table 3).[18]

Conclusions

In this study, 68.9% of the patients with no fracture healing had Vitamin D deficit, what was associated with increase in age and weight gain. That nobody showed other mechanic or biological background allows inquiries about the strong association between Vitamin D deficit and fracture lack of healing.

This study contributes with objective elements that facilitate identifying risk groups that could fail in fracture healing and, this way, encourages vitamin supplement implementation backed by Argentine bibliography on the backgrounds of its low costs and null risks at the time of managing patients with delayed bone union and Vitamin D deficit.[3,14.] This way, surgical treatment could be avoided in many of these patients.

Table 3. Conditions and drugs associated with Vitamin D deficit

- Osteoporosis
- Malabsorption syndrome: celiac disease, inflammatory intestinal disease, Crohn disease, bariatric surgery, radiation enteritis
- Chronic renal failure
- Hepatic failure
- Hyperparathyroidism
- Drugs: anticonvulsants, glucocorticoids, ketoconazole, cholestyramine, some treatments for AIDS
- Elderly with history of falls or non-traumatic fractures
- Obesity (defined by >30 kg/m2 body mass index)
- Granulomatous disease, lymphoma
- Chronic neurologic conditions: Parkinson's disease, multiple sclerosis, etc.
- Cancer
- Transplantation

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