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Effective Vitamin D Supplementation in Patients with Tibial Fracture

Suplementación efectiva de vitamina D en pacientes con fractura tibial

Sebastián Drago[1,2] Jose Miguel Rojas[1] Horacio Jiménez[1] Nicolás Gaggero[1] Rodrigo Olivieri[1] Piero Innocenti[1] Víctor Barrientos[3] Aquiles Jara[4]

[1] Department of Orthopedic Surgery, Hospital del Trabajador, Santiago, Chile
[2] Faculty of Medicine, Universidad de los Andes, Santiago, Chile
[3] Universidad Católica Silva Henríquez, Santiago, Chile
[4] Pontificia Universidad Católica de Chile, Santiago, Chile

Address for correspondence Sebastián Drago, MD, Hospital del Trabajador/Facultad de Medicina, Universidad de los Andes, Santiago, Chile (e-mail: sebadrago@gmail.com).

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Abstract

Objective To determine the prevalence of vitamin D deficiency and to evaluate the safety and effectiveness of a new method of cholecalciferol loading in adult patients with a tibial fracture.

Materials and Methods We recruited 56 consecutive patients with ages ranging from 18 to 65 years with tibial fracture who were admitted to our hospital for 1 year. We determined the level of 25-hydroxyvitamin D ([25 (OH)-D]) at admission and after supplementation with a weekly dose of 100,000 IU of cholecalciferol for 3 or 5 weeks in cases of insufficiency ([25 (OH)-D] between 20 ng/mL and29.9 ng/mL) or deficiency ([25 (OH)D] $<$ 20ng/mL) respectively. The prevalence of hypovitaminosis D, the percentage of vitamin D normalization, and the adverse effects were reported.

Results We evaluated 56 patients with tibia fractures; 98.1% presented hypovitaminosis D, and 28 (73,7%) and 10 (26,3%) showed deficit and insufficiency respectively. A total of 92.1% of the patients reached normal vitamin D levels after supplementation. No patient presented adverse effects.

Discussion The prevalence of vitamin D deficiency in our population was higher than the rates previously reported in the literature. The new vitamin D supplementation scheme proposed is safe and more effective than the one previously recommended. This supplementation scheme can be implemented in future randomized studies.

Conclusion The prevalence of hypovitaminosis D in Chilean adult patients with a tibial fracture was high (98.1%). The proposed vitamin D supplementation scheme was safe and effective.

Level of Evidence Therapeutic study. Level 2.

Keywords
- bone union
- vitamin D deficiency
- tibial fracture
- vitamin D supplementation

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Resumen

Objetivos Determinar la prevalencia de déficit de vitamina D, así como evaluar la seguridad y efectividad de un nuevo método de carga con colecalciferol en pacientes adultos con fractura de tibia.

Materiales y Métodos Se reclutaron a 56 pacientes consecutivos con edades entre 18 y 65 años con fractura de tibia ingresados en nuestro hospital durante 1 año. Se determinó el nivel de 25-hidroxivitamina D ([25(OH)-D]) al ingreso y tras suplementación con 100.000 UI semanales de colecalciferol, durante 3 o 5 semanas, en casos de insuficiencia ([25(OH)-D] entre 20 ng/mL y 29,9 ng/mL) o deficiencia ([25(OH)-D] $<$ 20 ng/mL), respectivamente. Se determinó la prevalencia de hipovitaminosis D, el porcentaje de normalización de [25(OH)-D], y los efectos adversos.

Resultados Se evaluaron 56 pacientes; 98,2% presentó hipovitaminosis D, y 28 (73,7%) y 10 (26,3%) presentaron déficit e insuficiencia, respectivamente. Tras la suplementación, 92,1% alcanzaron niveles [25(OH)-D] normales. Ningún paciente presentó efectos adversos.

Discusión La prevalencia de deficiencia de vitamina D en nuestra población fue mayor a la reportada en la literatura. Comprobamos que un esquema de suplementación en altas dosis de vitamina D es seguro, y más efectivo que los previamente recomendados. Este esquema de suplementación puede ser implementado en futuros estudios randomizados.

Conclusión La prevalencia de hipovitaminosis D en pacientes adultos chilenos con fractura de tibia fue alta (98,2%). El esquema de suplementación con vitamina D propuesto fue efectivo y seguro.

Nivel de Evidencia Estudio terapéutico. Nivel 2.

Palabras clave

- consolidación ósea
- deficiencia vitamina D
- fractura tibial
- suplementación vitamina D

Introduction

Vitamin D plays a role in the homeostasis of several physiological processes in the human body, particularly bone union.[1–4] Serological concentrations of 25-hydroxyvitamin D ([25(OH)-D]) $\geq$ 30 ng/mL are within normal ranges; values from 20 ng/mL to 29 ng/mL are insufficient, and those $<$ 20 ng/mL are deficient.[5,6]

Various studies have shown deficient plasma levels of vitamin D in 2% to 90% of the patients evaluated.[7] This range varies according to cut-off points and populations, with 37.3% and 88.1% of deficiency and insufficiency rates respectively.[7] In Chile, the prevalence of vitamin D deficiency has been determined among the pediatric population,[8] pre- and postmenopausal women,[9,10] healthy elderly people,[11] and elderly patients with hip fractures.[12]

The Endocrine Society[5] recommends a dose of 50,000 IU per os (PO) of vitamin D2 or D3 once a week for 8 weeks for adults with vitamin D deficiency, followed by a maintenance dose of 1,500 IU to 2,000 IU/day PO. This treatment reportedly normalizes [25(OH)-D] levels in up to 72% of healthy patients.[13–15]

The levels of vitamin D decrease during fracture healing.[16] Consistently, the weekly administration of 50,000 IU resulted in a low rate of normalization of the levels of [25(OH)-D] in fracture patients.[13,17] The metabolic change generated by a traumatic injury may require a higher supplementation dose to normalize the values and avoid complications regarding bone healing.[3,18,19]

The effectiveness of vitamin D supplementation in bone union remains controversial; some clinical series and a systematic review[1] showed no clear benefits of correcting [25(OH)-D] deficiency[20] or a decrease in complication rates.[17]

Toxic [25(OH)-D] levels are $>$ 150 ng/mL.[21] In contrast, it has been suggested that cholecalciferol doses of 100,000 IU/week for 5 weeks are safe and normalize vitamin D levels in a higher percentage of patients.[22]

Based on these findings, vitamin D supplementation with a dose higher than usual in adult patients with fractures could benefit bone healing. The present pilot study aims to determine the prevalence of hypovitaminosis D and the safety and effectiveness of an established dose of vitamin D in patients with tibial fractures. We hypothesize that the weekly administration of 100,000 IU of cholecalciferol effectively normalizes serological values without generating toxic [25(OH)-D] levels.

Materials and Methods

The present is a study involving a prospective cohort of 56 consecutive patients aged 18 to 65 years who presented a tibial fracture and were admitted to a level-1 trauma center from May 1st, 2017, to April 30, 2018. The institutional ethics committee approved the study.

The recruited patients had a tibial fracture treated with an intramedullary nail. After admission to the emergency

department, we invited them to participate in the study. Those who agreed signed an informed consent form. The following subjects were excluded from the sample: those with a glomerular filtration rate < 60 mL/minute, history of kidney disease or calculi, under current supplementation with multivitamins, history of cancer, pathological bone fracture, difficulty receiving oral treatment, preexisting conditions that alter vitamin D metabolism (liver failure, parathyroid disorders, hypocalcemia, or hypercalcemia), allergy or contraindications to vitamin D, pregnant patients, those with no serological sample for the determination of the level of [25(OH)-D], subjects with normal [25(OH)-D] levels (≥ 30 ng/mL), and patients who refused to participate in the study.

We enrolled 56 patients, and 18 (32.1%) were excluded, including 1 (1.8%) who presented normal levels of vitamin D at admission, 1 (1.8%) who refused treatment, and 16 (28.6%) who did not comply with the stipulated timeframe for cholecalciferol administration (►**Figure 1**). The incidence of hypovitaminosis D was of 98.2% (55/56 patients). The analysis included 38 patients, 33 (86.9%) men and 5 (13.1%) women. Their average age was 40 years (range: 21 to 90 years; standard deviation [SD] = 14.4 years) (►**Table 1**).

Serological levels of [25(OH)-D] were obtained in the emergency department or up to 2 days after admission using chemiluminescence (ADVIA Centaur XP, Siemens Healthineers, Erlangen, Germany). The reference values were ≥ 30 ng/mL. Levels ranging from 20 ng/mL to 29 ng/mL and those lower than 20 ng/ml characterized insufficiency and deficiency respectively.

At the outpatient care center, a paramedic technician administered a dosis of 100,000 IU of cholecalciferol once a week for 3 weeks to patients with vitamin D deficiency and for 5 weeks to patients with vitamin D deficiency. Each dose was recorded at the time of administration. A serum sample was collected 4 days to 2 weeks after the last administration of cholecalciferol to evaluate the level of [25(OH)-D] after the supplementation.

The Shapiro-Wilk test was used to analyze the normal distribution of continuous variables. The parametric variables were expressed as mean ± SD. The Student *t*-test was used to analyze the parametric variable [25(OH)-D] levels

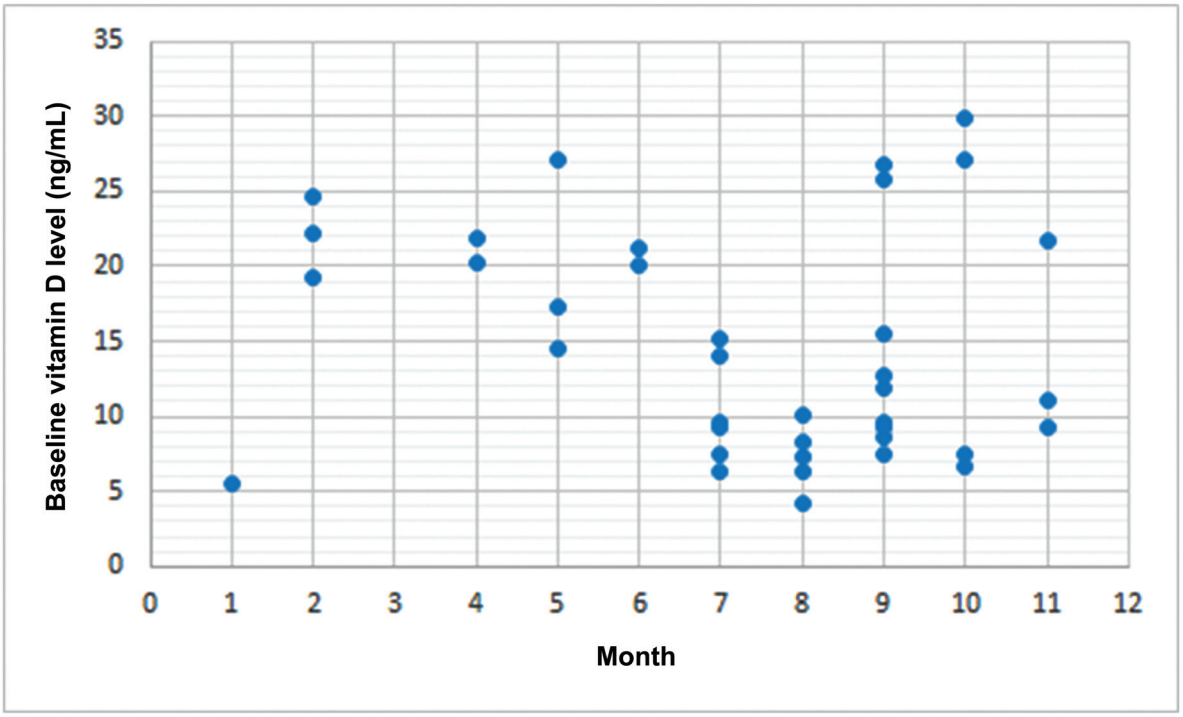

Fig. 1 Baseline vitamin D levels (ng/mL) per month.

Table 1 Sociodemographic variables of the study sample

	Gender		Total	Statistical analysis
	Male	Female		
Frequency	33 (86.9%)	5 (13.1%)	38 (100%)	*$p < 0.05$
Age in years: mean(± standard deviation)	42(± 14.9)	35(± 14.1)	40(± 14.4)	**$p = 0.33$

Notes: *Chi-squared test (goodness-of-fit test). **Student *t*-test (independent samples).

Table 2 Baseline and postsupplementation serological vitamin D levels

	N (%)	Baseline level of vitamin D: mean (± standard deviation)	Postsupplementation level of vitamin D: mean (± standard deviation)	Statistical analysis
Insufficiency	10 (26.3%)	24.84(± 2.97)	49.19(± 10,38)	$^{*}p < 0.05$
Deficiency	28 (73.7%)	10.89(± 4.53)	41.98(± 10,87)	$^{*}p < 0.05$
Total	38 (100%)	14.56(± 7.47)	43.88(± 12,67)	$^{*}p < 0.05$

Note: *Student *t*-test (independent samples).

after the supplementation. Chi-squared tests were used to analyze the categorical variables. Statistical significance was set at $p < 0.05$. The statistical analysis was performed using the Stata (StataCorp LLC, College Station, TX, United States) software, version 12.0.

Results

Among our patients, 28 (73.7%) and 10 (26.3%) had vitamin D deficiency and insufficiency respectively (►**Table 2**). The baseline levels of vitamin D showed a tendency to decrease during winter (►**Figure 1**).

Most patients (35/38; 92.1%) presented normal serological concentrations of vitamin D. The postsupplementation levels were significantly higher than the baseline levels for the entire sample (14.56 ng/mL versus 43.88 ng/mL; $p < 0.05$), as well as in the insufficiency subgroup (24.84 ng/mL versus 49.19 ng/mL; $p < 0.05$) and the deficiency subgroup (10.89 ng/mL versus 41.98 ng/mL; $p < 0.05$) (►**Table 2**). All patients (3; 7.9%) with abnormal postsupplementation concentrations had baseline [25(OH)-D] levels lower than 10 ng/mL: in one of them, the postsupplementation [25(OH)-D] level was of 25.9 ng/mL, while the remaining 2 subjects still presented deficient values, although higher than 10 ng/mL (►**Table 2**).

All subjects presented [25(OH)-D] levels lower than 80 ng/mL after the administration of cholecalciferol. There were no treatment-related adverse effects, and no patients withdrew from the study due to adverse effects secondary to the intervention.

Discussion

The prevalence of vitamin D deficiency is highly variable among the published studies, ranging from 2% to 90%.[7,23] Several factors influence this prevalence, including age, ethnicity, gender, seasonality, comorbidities, and serological cut-off point.[7]

The dosage for vitamin D normalization (30 ng/mL) is also debatable. The National Academy of Medicine (NAM), formerly called the Institute of Medicine (IoM),[6] and the Endocrine Society[5] recommends the administration of [25(OH)-D] in dosages of 50,000 IU PO per week or 6,000 IU PO per day until serological normalization, followed by a daily maintenance dose of 1,000 IU to 2,000 IU PO.

Despite this recommendation, the supplementation scheme was partially effective in our population of interest. A study[13] in trauma patients showed normalization of serological vitamin D levels in 54% and 0% of those with insufficiency and deficiency respectively after a weekly supplementation of 50,000 IU. These findings suggest that this dosage is ineffective.

In some studies, vitamin D supplementation with higher doses, of up to 600,000 IU PO per month, resulted in no hypercalcemia or other adverse effects,[6,24,25] and led to the effective normalization of plasma levels.[24] As such, we instituted a dosage of 100,000 IU PO per week for 3 weeks in subjects with vitamin D insufficiency and for 5 weeks in those with deficiency. This scheme resulted in a high normalization rate in our study population (92.1%) with no secondary adverse effects. The plasma levels of [25 (OH)-D] were always lower than 70 ng/ml, which is consistent with the lack of toxicity due to hypervitaminosis D, which is usually observed with serological concentrations above 150 ng/mL.[5,21]

Few reports associate vitamin D deficiency with bone union. Evaluating fusion in spinal arthrodesis after 1 year, Ravindra et al.[26] showed a longer time until union in patients with [25(OH)-D] deficiency. In addition, they identified hypovitaminosis D as an independent risk factor for non-union (odds ratio [OR]: 3.4).

Brinker et al.[20] investigated a consecutive series of 683 patients, including 37 with unexplained non-union, and observed a rate of hypovitaminosis D of 68% in this subgroup of patients. Interestingly, some achieved bone union after [25 (OH)-D] supplementation and no surgical reintervention.

In contrast, normal vitamin D levels in patients with fractures are not decisive in reducing associated complications from bone union issues and do not lower the probability of reintervention for the same cause.[17] Per these findings, some systematic reviews and meta-analyses[1,27,28] have failed to objectively identify the benefit of vitamin D supplementation for bone healing. However, studies are scarce, with small populations, high sample heterogeneity, and use supplementation schemes ineffective in normalizing vitamin D levels.

The main strengths of our study are its prospective design, the follow-up of 100% of the patients meeting the inclusion criteria, the delivery of all doses assigned to each patient individually by a paramedic technician, and the administration of a new, safe, and effective scheme for vitamin D

supplementation. Its weaknesses are the lack of randomization and a control group, which reduce the power of the information obtained, and a high percentage of patients leaving the study (28.6%) and not completing the supplementation scheme.

This is the first part of a comparative study to analyze the effect of vitamin D supplementation on bone healing in patients with tibial fractures. To do so, we first determined the prevalence of hypovitaminosis D in our population. Next, we demonstrated a safe and effective supplementation scheme, which will enable future comparisons with a group not treated with vitamin D.

Conclusion

There is a high prevalence of vitamin D deficiency in adult patients with tibial fractures. The new cholecalciferol supplementation scheme in patients with tibial fracture is effective and safe. The prevalence observed and the effectiveness of the dosage administered will help the development of prospective studies evaluating the benefit of vitamin D supplementation in bone union after tibial fracture.

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