



Influence of Hypovitaminosis D on the Occurrence of Fractures*

Influência da hipovitaminose D na ocorrência das fraturas

Cleandro Augusto Ribeiro do Valle¹ Luiz Alfredo Furtado Pedri¹ Guilherme Bigonha Pires¹
Mariella Soares Blanco² Bruna Soares Paula² Carlos Delano Mundim Araújo^{1,3}

¹ Department of Orthopedics and Traumatology, Hospital das Clínicas Samuel Libânio, Universidade do Vale do Sapucaí (UNIVÁS), Pouso Alegre, Minas Gerais, MG, Brazil

² Faculdade de Ciências Médicas Dr. José Garcia Coutinho, Universidade do Vale do Sapucaí (UNIVÁS), Pouso Alegre, Minas Gerais, MG, Brazil

³ Centro Universitário Atenas (UNIATENAS), Paracatu, Minas Gerais, MG, Brazil

Address for correspondence Carlos Delano Mundim Araújo, M.D, Hospital das Clínicas Samuel Libânio, Rua Comendador José Garcia, 777, Centro, Pouso Alegre, Minas Gerais, MG, 37550-000, Brazil (e-mail: drcdelano@hotmail.com).

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Abstract

Objective To measure the levels of vitamin D in patients hospitalized for fractures and to evaluate its relationship with fractures.

Methods A primary, analytical, cross-sectional, non-interventional, observational, controlled study was conducted in humans. The serum measurement of: vitamin D, parathyroid hormone (PTH), calcium, phosphorus, magnesium and albumin was performed in 49 patients who were consecutively hospitalized for surgery due to fracture(s) (study group), and in 50 patients without fractures, from the various outpatient clinics, and who underwent routine tests (control group).

Results The mean level of 25-hydroxyvitamin D (25[OH]D) in patients with fractures was of 23.78 ± 8.01 ng/mL (61.22% of patients with fractures had hypovitaminosis D). The mean 25(OH)D of the control group was of 37.52 ± 9.21 ng/mL (10% of the patients had hypovitaminosis D). Most cases of hypovitaminosis (96%) did not course with secondary hyperparathyroidism (mean PTH = 41.80 ± 22.75 pg/mL).

Conclusion Hypovitaminosis D was found in a significant percentage (61.22%) of the patients who suffered fractures. Further studies on the subject are needed to better understand the influence of hypovitaminosis D on the occurrence of fractures, as well as the benefits of vitamin D supplementation in these patients.

Keywords

- ▶ vitamin D
- ▶ vitamin D deficiency
- ▶ osteoporosis
- ▶ hip fractures
- ▶ fracture healing

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Resumo

Palavras-chave

- vitamina D
- deficiência de vitamina D
- osteoporose
- fraturas do quadril
- consolidação da fratura

Objetivo Dosar a vitamina D nos pacientes internados por fratura e avaliar sua relação com as fraturas.

Métodos Realizou-se estudo primário, analítico, transversal, não intervencional, observacional, controlado, em seres humanos. Fez-se a dosagem sérica de: vitamina D, paratormônio(PTH), cálcio, fósforo, magnésio e albumina em 49 pacientes que foram internados consecutivamente para cirurgia devido a fratura(s) (grupo de estudo), e em 50 pacientes, dos diversos ambulatorios, sem fraturas, e que realizaram exames de rotina (grupo de controle).

Resultados A média de 25-hidroxivitamina D (25[OH]D) nos pacientes com fraturas foi de $23,78 \pm 8,01$ ng/mL (61,22% dos pacientes com fraturas apresentaram hipovitaminose D). A média de 25(OH)D do grupo de controle foi de $37,52 \pm 9,21$ ng/mL (10% dos pacientes apresentaram hipovitaminose D). A maioria dos casos de hipovitaminose (96%) não cursou com hiperparatireoidismo secundário (média do PTH = $41,80 \pm 22,75$ pg/mL).

Conclusão A hipovitaminose D foi encontrada em um percentual expressivo (61,22%) dos pacientes que sofreram fraturas. Mais estudos sobre o assunto são necessários para se compreender melhor a influência da hipovitaminose D na ocorrência das fraturas e os benefícios da suplementação com vitamina D nesses pacientes.

Introduction

The study of vitamin D (VIT D) and the consequences of its deficiency in the body are relatively new topics, and they became known after the Industrial Revolution, when the rural population migrated to the urban centers.

The main known function of VIT D is to keep calcium and serum phosphorus concentrations within normal physiological limits to maintain most metabolic functions, neuromuscular transmission, and bone mineralization. Most often, the changes due to VIT D deficiency are subclinical.¹

Hypovitaminosis D (HVD) leads to decreased mineralization of the bone matrix, which can lead to rickets in childhood and osteomalacia in adults, as well as worsening of cases of osteoporosis. Vitamin D plays a fundamental role in the metabolic pathway of calcium, and its supplementation is associated with increased bone mineral mass and the prevention of fractures. Fractures due to osteoporosis result in high costs, with a treatment comparable to those for cardiovascular diseases.²

Approximately one third of the world's population has levels of 25-hydroxyvitamin D (25[OH]D) lower than 20 ng/mL, which may not be ideal to maintain good bone health.³ There is evidence that HVD is the most common nutritional deficiency in the world.⁴ Traditionally, Brazil was considered a place where there were no cases of HVD, because it is a tropical, sunny country, with wide exposure of the population to the sun. However, recent studies have demonstrated the lack of VIT D in the most diverse age groups and places in the country.⁵⁻¹⁰ Hypovitaminosis D, which plagues the world population and even Brazil may have occurred due to changes in habits such as protection against the sun protection, the use of sunscreen, the season of the year and lower exposure to the sun in cold regions, as well as food shortages.

It is well established in the literature that HVD predisposes to bone fragility and influences postural and dynamic balance, favoring the occurrence of fractures. However, until the beginning of the present study, no studies on the dosage of VIT D in the population of our region (the southern part of the state of Minas Gerais, Brazil) had been found, nor studies on the influence of VIT D on the occurrence of fractures in the Brazilian population. The aim of the present study was to measure the levels of VIT D in fractured patients and evaluate its relationship with fractures.

Methods

A primary, analytical, cross-sectional, non-interventional, observational, controlled study was conducted in humans. We consecutively selected 49 patients with fractures (study group) (1 patient in the study group was excluded due to renal alteration) with surgical indication, and 50 patients without fractures (control group), older than 18 years of age, without any restrictions regarding color or gender, who agreed to participate in the study. The patients in the study group were selected consecutively to their hospitalization in the orthopedics and traumatology ward of our institution; and the tests were collected along with routine preoperative blood tests. The patients in the control group were selected from the outpatient clinics of the various specialties in the same hospital, provided they had any outpatient indication of blood collection. We excluded: patients hospitalized for more than 24 hours; undergoing VIT D replacement; with endocrine, genetic or metabolic diseases capable of altering the normal metabolism of VIT D (osteogenesis imperfecta, Paget disease); with acute or chronic renal failure; with pathological fractures of neoplastic origin or under neoplastic treatment; with malnutrition; with psychiatric eating disorders (bulimia and

anorexia); those undergoing bariatric surgery or bowel resection; those with small bowel diseases, biliary or hepatic tract disease, and intestinal exocrine pancreatic insufficiency that interfere with fat absorption (sprue, amyloidosis, etc.); and patients using medications that hinder the resorption of fat (orlistat, cetilistat and the like).

All patients who spontaneously agreed to participate in the study signed a free and informed consent form. The study was approved by the Ethics Committee under CAAE 94612618.6.0000.5102. The patients were initially submitted to sociodemographic data collection, body weight and height (in meters) measurements, and filled out a questionnaire on habits of protection against the sun and smoking. Next, they were submitted to peripheral venous puncture and blood collection for dosage of 25(OH)D, parathyroid hormone (PTH), total and ionized serum calcium, phosphorus, magnesium and albumin. The 25(OH)D and PTH were dosed by the chemiluminescence method. Hypovitaminosis was characterized according to the current position of the Brazilian Society of Clinical Pathology and Laboratory Medicine (Sociedade Brasileira de Patologia Clínica e Medicina Laboratorial, SBPC/ML, in Portuguese) and the Brazilian Society of Endocrinology and Metabology (Sociedade Brasileira de Endocrinologia e Metabologia, SBEM, in Portuguese).¹¹ Thus, levels of 25 (OH)D > 20 ng/mL were considered the normal value for a healthy population (aged up to 60 years); between 30 ng/mL and 60 ng/mL, the recommended value for risk groups such as: elderly, pregnant women, osteoporosis patients, those with a history of falls and fractures, and patients with secondary causes of osteoporosis (diseases and medications); levels > 100 ng/mL were considered risk of intoxication.

The data were tabulated in Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, US) spreadsheets and submitted to statistical analysis. Central trend measurements were used for the quantitative variables, and absolute and relative frequencies were used for the categorical variables. The Minitab (Minitab, LLC, State College, PA, US) software, version 18.1, and the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 22.0, were used. The significance level adopted for the statistical tests was of 5% ($p < 0.05$).

Results

The groups were similar in terms of body mass index (BMI), age and gender (►Tables 1 and 2). In the study group, there

Table 2 Comparison of groups with respect to gender

Group	Male	Female	Total	p
Study	31 (63%)	18 (37%)	49 (100%)	0.150
Control	25 (50%)	25 (50%)	50 (100%)	

Note: Fischer exact test.

Table 3 Comparison between the degree of protection against and exposure to the sun and smoking between the groups

Protection against the sun	Control	Study	p
No	23	23	
Sunscreen and/or clothing	27	26	1
Only sunscreen	0	0	
Total	50	49	
Smoking			
Yes	10	12	
No	40	37	0.483
Total	50	49	
Exposure to the sun			
Daily	37	32	
Occasional	13	19	1
Total	50	49	

Note t-Test.

were 15 (30.61%) elderly (aged > 60 years) patients, and 14 of them (93.33%) had VIT D levels < 30 ng/mL. In the control group, there were 18 (36%) elderly people, and 5 of them (27.77%) had VIT D levels < 30 ng/mL.

There was also a similarity between the skin color of the groups, which was predominantly white in more than 80% of the population studied (82% of white subjects in the control group, and 87.75% in the study group).

The groups also resembled each other in degree of skin protection, smoking and exposure to the sun (►Table 3).

The mean level of PTH of the control group was of 39 (± 23.70) pg/mL, and that of the study group was of 44.60 (± 21.80) pg/mL (VN = 18.5 pg/mL to 88 pg/mL). Evaluating both groups, only two cases of hyperparathyroidism secondary to HVD were observed.

Table 1 Distribution of the sample considering age and body mass index

	Group	N	Mean	Standard deviation	Minimum	Maximum	p
Age	Control	50	50.40	21.3	20	89	
	Study	49	50.30	21.5	18	90	0.983
Body mass index	Control	50	26.13	3.69	18.39	35.1	
	Study	49	27.10	5.19	18.13	45.49	0.289

Note: t-test.

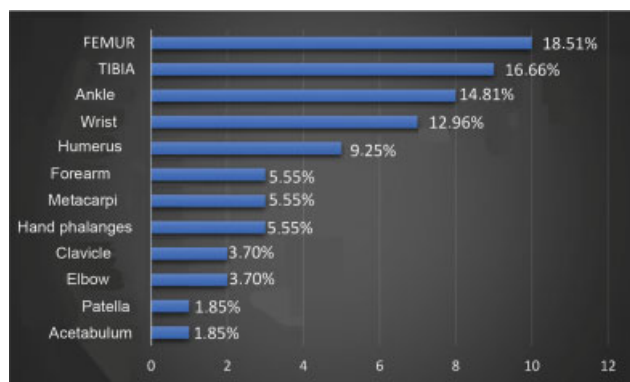


Fig. 1 Distribution of fractures (low- and high-energy traumas).

Table 4 25-hydroxyvitamin D dosage: comparison of the groups by the t-test

Groups	N	Mean (ng/mL)	Standard deviation	p
Study	49	23.78	8.01	0.00*
Control	50	37.52	9.21	

Note: *Statistical significance.

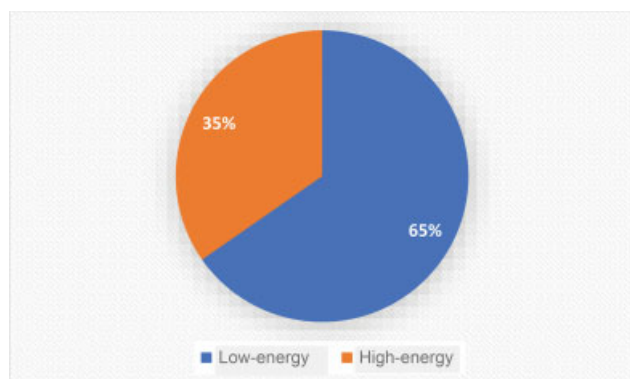


Fig. 2 Distribution of trauma energy (percentage of patients).

FA total of 54 fractures were observed in 49 patients, and 53.68% of them occurred in the lower limbs (►Figure 1). The mean level of 25(OH)D of the groups can be observed in Table 4. In total, HVD was present in 30 (61.22%) patients with fractures (study group), and in 5 (10%) patients in the control group.

The distribution of fractures according to the intensity of the energy of the trauma is demonstrated in ►Figure 2, and its relationship with the degree of sufficiency of 25(OH)D is shown in ►Figure 3. The correlation between HVD and the occurrence of fractures is found in ►Table 5.

Discussion

Studies, including Systematic reviews¹²⁻¹⁶ evaluated the dosage of VIT D in fractures and evidenced the importance of HVD in their occurrence (prevalence: between 40% and 100% of the cases).¹²⁻¹⁶ In the present study, HVD was

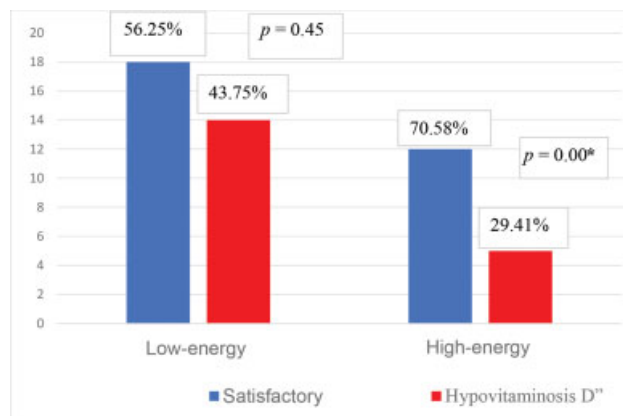


Fig. 3 Distribution of fractures according to trauma intensity and degree of vitamin D sufficiency (Fischer exact test). Note: *Statistical significance.

Table 5 Correlation between fractures and vitamin D by the Spearman coefficient

N (STUDY + CONTROL)	Spearman r	p
99	0.668	0.00*

Note: *Statistical significance.

observed in 30 (61.22%) patients with fractures. There was a statistically significant difference regarding the dosage of VIT D between the groups, which enabled us to speculate that HVD was a facilitating agent for fractures (►Tables 4 and 5). Most studies mainly evaluate the elderly and post-menopausal women, who are populations at risk for osteoporosis;⁷ therefore, these studies evaluate low-energy fractures, because they represent the highest percentage of fractures.^{12,13,16} Fractures resulting from low-energy trauma tend to be spontaneous, due to falls from standing height, or to tortional mechanisms, and they mainly occur in the proximal femur, distal radius and spine,^{12,16,17} especially in the elderly, among whom an episode within their own home is frequent. They are commonly unique lesions and are the ones that mostly require surgical treatment.¹³ In studies that exclusively evaluated low-energy fractures, a higher frequency of fractures of the proximal femur^{12,16} or wrist was found.¹⁵ The present study evaluated all fractures that arrived consecutively in the emergency room, that is, low- and high-energy fractures, which were included in the study as long as they had a surgical indication. On the one hand, this could be a limiting factor of the present study, since fractures without surgical indication were not catalogued; however, it venous punctures that for the exclusive purpose of the present study were avoided. Low-energy fractures were also predominant in the present study (►Figure 2), but, unlike other publications^{12,15,16}, the highest incidence of low energy fractures occurred in the ankles (8 cases; 14.81% of the fractures). This discrepancy may be justified by the fact that, in the present study, unlike other studies^{12,13,15,16}, the male population composed most of the sample (63% of the

cases), and also because the mean age (50.30 years) was much lower than that found in other studies. Therefore, the sample of the present study was composed of a majority of patients of the male gender and of an age group in which proximal fractures of the femur are less frequent.

High-energy fractures are usually due to accidents that occur outside the home, such as car accidents; they are less evaluated, but these patients also tend to have a very high HVD index.¹⁴ In the fractures caused by high-energy trauma in the present study, there were 29.41% of cases of HVD (–Figure 3).

Although the effect of VIT D on a fracture that already occurred is unknown and there is no concrete evidence that VIT D accelerates the consolidation process, its effect of increasing the vascularization of the bone callus,¹⁸ increasing bone strength and mineral density, as well as increasing the volume of the bone callus, is undeniable.^{10,14} In addition, a study reported¹⁹ HVD in 83% of the cases of pseudarthrosis and consolidation delays.¹⁹ In a retrospective study, Gorter et al.¹⁵ evaluated 617 patients with fractures (40% of prevalence of HVD) and observed that fracture consolidation was influenced by the status of VIT D at the time of the fracture.

It is customary that, in the case of fractures, the levels of VIT D fall sharply due to their consumption in the focus of the fracture, especially if the initial level is already low. This fall occurs between one and three weeks after the fracture.¹⁴ The initial levels of VIT D fall around 20% at the end of the first week.²⁰ This detail is considered a major factor in studies on HVD prevalence in fractures, but a significant part of the studies^{12,13,15,16} does not mention the exact moment the levels of 25(OH)D were assessed. In the present study, this assessment occurred within 24 hours of the fracture. This detail also has importance in order to supplement more rigorously the patient with HVD who suffers a fracture.

Falls represent a marker of morbidity and mortality, especially in the elderly, and in about 10% of the times they cause fractures.²¹ In Brazil, osteoporosis mainly affects women from metropolitan regions.²² There is a high prevalence of HVD, especially among the elderly. In the present study, we observed that 93.33% of the elderly with fractures presented HVD. Fractures resulting from falls, especially in the hip, lead to death in about 20% of the cases and, in 50% of the non-fatal cases, they lead the elderly to become dependent.²³ The treatment of HVD in the elderly reduces falls by 20%, and in every 15 patients treated, a fall is prevented.²⁴ Adequate levels of VIT D reduce the risk of fractures by 20%.²⁵ It was also observed that the associated use of VIT D and calcium decreased by 15% the chance of developing fractures in general, and decreased hip fractures by 30%.²⁶

The orthopedic surgeon should be prepared to recognize HVD and know how to track and treat it, or give the patient a referral.²⁷ In the daily practice, patients who are hospitalized with fractures to undergo surgical treatment have preoperative tests that usually do not involve the measurement of VIT D. Given the importance of VIT D in muscle strength and balance, and its role in fracture consolidation (although questionable), it is suggested that, whenever possible, the measurement of the levels of VIT D (a relatively expensive examination, not covered by the Brazilian Unified Health System [SUS, in Portuguese]), should be part of the

preoperative routine, especially in the elderly or postmenopausal women with fractures, as well as its replacement, if necessary. Hypovitaminosis D is present in all age groups and population groups, especially among the Brazilian elderly, who depend on skin synthesis to obtain sufficiency.^{5,6} Although exposure to the sun can increase the levels of VIT D, this organic management for the sufficiency of VIT D has been shown to be unfavorable in view of the potential carcinogenic effects of ultraviolet rays and changes in habits (protection against the sun), and also because the seasons and geographic latitude may prevent appropriate exposure to sunlight. Therefore, dietary supplementation has been the preferred method to manage VIT D levels. A study²⁴ conducted with healthy young adults showed that the use of VIT D is safe and does not have severe side effects, even in doses that are ten times greater than the recommended dose. The policy of supplementation of foods such as milk, orange juice and butter with VIT D proved to be efficient to increase the plasma concentrations of 25(OH)D in the countries in which it is enforced.⁶ Similar policies could also be used in Brazil, with potential benefits for our geriatric population. Given the low cost, safety and demonstrated benefit of higher concentrations of 25(OH)D, VIT D supplementation should be a public health priority.²⁸ Although VIT D supplementation is considered inexpensive in food, in Brazil it is added to specific foods that are not part of the routine feeding of the elderly. Until a broader VIT D supplementation becomes a reality in Brazil, traumatologists have a duty to know and correct HVD, especially in the elderly treated with fractures. The events of intoxication by VIT D are rare. It should be considered that, in selected cases, supplementation, although somewhat indiscriminate (it is not always possible to dose VIT D), can bring benefits that would overcome the risks of its deficiency and the high costs related to fractures.

Conclusion

Hypovitaminosis D was found in a significant percentage (61.22%) of the patients who suffered fractures. Further studies on the subject are needed to better understand the influence of HVD on the occurrence of fractures and the benefits of VIT D supplementation in these patients.

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Conflict of Interests

The authors have no conflict of interests to declare.

References

- 1 Maeda SS, Fortes EM, Oliveira UM, Borba VC, Lazaretti-Castro M. Hypoparathyroidism and pseudohypoparathyroidism. *Arq Bras Endocrinol Metabol* 2006;50(04):664–673
- 2 Aziziye R, Amin M, Habib M, et al. The burden of osteoporosis in four Latin American countries: Brazil, Mexico, Colombia, and Argentina. *J Med Econ* 2019;22(07):638–644
- 3 Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO) A importância da vitamina D na saúde da mulher.

- São Paulo: FEBRASGO; 2018. (Série Orientações e Recomendações FEBRASGO, n.º 14)
- 4 Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc* 2013;88(07):720–755
 - 5 Bandeira F, Griz L, Freese E, et al. Vitamin D deficiency and its relationship with bone mineral density among postmenopausal women living in the tropics. *Arq Bras Endocrinol Metabol* 2010;54(02):227–232
 - 6 Saraiva GL, Cendoroglo MS, Ramos LR, et al. Prevalência da deficiência, insuficiência de vitamina D e hiperparatireoidismo secundário em idosos institucionalizados e moradores na comunidade da cidade de São Paulo, Brasil. *Arq Bras Endocrinol Metabol* 2007;51(03):437–442
 - 7 Peters BS, dos Santos LC, Fisberg M, Wood RJ, Martini LA. Prevalence of vitamin D insufficiency in Brazilian adolescents. *Ann Nutr Metab* 2009;54(01):15–21
 - 8 Paiva CAC, Bettinelli LA, Portela MR, Pasqualotti A. Prevalência de hipovitaminose D e sua severidade em idosos institucionalizados no município de passo fundo. *Rev Cont Saúde* 2011;10(20):1243–1250
 - 9 Santos EP Junior, Fernandes DC, Almeida AT, Borges FA, Novaes JA. Epidemiologia da vitamina D. *Reva Cient ITPAC, Araguaína* 2011;4(03). Disponível em: <https://assets.itpac.br/arquivos/Revista/43/2.pdf>
 - 10 Maeda SS, Borba VVC, Camargo MB, et al. Recomendações da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) para o diagnóstico e tratamento da hipovitaminose D. *Arq Bras Endocrinol Metabol* 2014;58(05):411–433
 - 11 Sociedade Brasileira de Patologia Clínica e Medicina Laboratorial (SBPC/ML) e Sociedade Brasileira de Endocrinologia e Metabologia. (SBEM): Posicionamento de Intervalos de Referência da Vitamina D – 25(OH)D. [acesso em 03/02/2019]. Disponível em: <http://www.sbpcc.org.br/noticias-e-comunicacao/novos-intervalos-de-referencia-de-vitamina-d/>
 - 12 Simonelli C, Weiss TW, Morancey J, Swanson L, Chen YT. Prevalence of vitamin D inadequacy in a minimal trauma fracture population. *Curr Med Res Opin* 2005;21(07):1069–1074
 - 13 Mow TC, Stokes CM, Sutherland AG. Patients presenting with fractures are likely to be vitamin D deficient: are we getting enough sun? *ANZ J Surg* 2015;85(10):766–769
 - 14 Sprague S, Petrisor B, Scott T, et al. What is the role of vitamin D supplementation in acute fracture patients? A systematic review and meta-analysis of the prevalence of hypovitaminosis D and supplementation efficacy. *J Orthop Trauma* 2016;30(02):53–63
 - 15 Gorter EA, Krijnen P, Schipper IB. Vitamin D status and adult fracture healing. *J Clin Orthop Trauma* 2017;8(01):34–37
 - 16 Devigili N Jr, Botega L, Back SRS, Stipp WN, Back Netto M. Prevalência da deficiência de vitamina D em pacientes com fraturas ocasionadas por trauma de baixa energia. *Rev Bras Ortop* 2019;54(01):69–72
 - 17 Milzman DP, Boulanger BR, Rodriguez A, Soderstrom CA, Mitchell KA, Magnant CM. Pre-existing disease in trauma patients: a predictor of fate independent of age and injury severity score. *J Trauma* 1992;32(02):236–243, discussion 243–244
 - 18 Omeroğlu S, Erdoğan D, Omeroğlu H. Effects of single high-dose vitamin D3 on fracture healing. An ultrastructural study in healthy guinea pigs. *Arch Orthop Trauma Surg* 1997;116(1-2):37–40
 - 19 Brinker MR, O'Connor DP, Monla YT, Earthman TP. Metabolic and endocrine abnormalities in patients with nonunions. *J Orthop Trauma* 2007;21(08):557–570
 - 20 Ettehad H, Mirbolook A, Mohammadi F, Mousavi M, Ebrahimi H, Shirangi A. Changes in the serum level of vitamin d during healing of tibial and femoral shaft fractures. *Trauma Mon* 2014;19(01):e10946
 - 21 Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. *J Steroid Biochem Mol Biol* 2004;89-90(1-5):497–501
 - 22 Pinheiro MM, Ciconelli RM, Jacques NO, Genaro PS, Martini LA, Ferraz MB. O impacto da osteoporose no Brasil: dados regionais das fraturas em homens e mulheres adultos - The Brazilian Osteoporosis Study (BRAZOS). *Rev Bras Reumatol* 2010;50(02):113–120
 - 23 Mello RG, Schneider RH, Collares FM, Dalacorte RR. Vitamina D e prevenção de quedas em idosos: uma revisão sistemática. *Sci Med (Porto Alegre)* 2010;20(02):200–206
 - 24 Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004;116(09):634–639
 - 25 Zittermann A, Gummert JF. Nonclassical vitamin D action. *Nutrients* 2010;2(04):408–425
 - 26 Weaver CM, Alexander DD, Boushey CJ, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int* 2016;27(01):367–376
 - 27 Nino S, Soin SP, Avilucea FR. Vitamin D and Metabolic Supplementation in Orthopedic Trauma. *Orthop Clin North Am* 2019;50(02):171–179
 - 28 Bischoff-Ferrari HA, Conzelmann M, Stähelin HB, et al. Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? *Osteoporos Int* 2006;17(05):656–663