# **Original Article**

# Low serum vitamin D levels are not associated with pseudoarthrosis and implant loosening in ankle arthrodesis: a retrospective cohort study

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# Abstract

Objective: Analyze the relationship between hypovitaminosis D and pseudoarthrosis and implant loosening after ankle arthrodesis.

**Methods:** Retrospective and observational study using data extracted from the TriNetX international platform, including patients of both sexes, aged  $\geq$  18 years, undergoing tibiotarsal or tibiotalocalcaneal arthrodesis between 2016 and 2020, with at least one level of 25-hydroxyvitamin D in the perioperative period and one year of follow-up. Patients were divided into two groups: vitamin D deficiency ( $\leq$  20 ng/ml) and no deficiency (> 20 ng/ml). Statistical analyses used logistic regression with propensity score matching, in addition to chi-square, Student's t, and Log-rank tests.

**Results:** Three hundred and six patients were selected for the study. After pairing, 72 patients were analyzed in each group. There was no statistically significant difference between the groups (adjusted OR = 0.878; 95% CI: 0.333-2.309; p = 0.7912). Similarly, there was no association between vitamin D deficiency and implant loosening/synthesis failure (adjusted OR = 1.017; 95% CI: 0.394-2.623; p = 0.9723).

**Conclusion:** The results indicate that vitamin D deficiency is not significantly associated with the risk of pseudoarthrosis or implant loosening in the short term. While supplementation may be beneficial, its clinical impact remains to be further investigated.

Level of evidence: II, Observational study.

Keywords: Pseudoarthrosis; Vitamin D deficiency; Arthrodesis; Ankle; Healing.

### Introduction

The high prevalence of vitamin D deficiency is considered a concern worldwide, as it contributes to osteopenia, osteomalacia, and worsens osteoporosis<sup>(1)</sup>. Low vitamin D levels can dysregulate the homeostasis of the bone healing process in fractures and procedures such as ankle arthrodesis<sup>(2)</sup>.

Vitamin D is synthesized in the skin under the influence of ultraviolet radiation and hydroxylated in the liver, forming calcidiol 25(OH)D, and later in the kidneys to its most

biochemically active form:  $1,25(OH)_2D_3^{(3)}$ . The active form binds to receptors in the intestine, kidney, parathyroid glands, and bone, regulating plasma calcium and phosphorus levels and subsequently bone mineralization and consolidation<sup>(4)</sup>.

Recently, hypovitaminosis D has also been associated with poor clinical outcomes after orthopedic interventions, especially in spinal arthrodesis<sup>(5,6)</sup>. However, the relationship between hypovitaminosis D and clinical outcomes after arthrodesis procedures, including those performed on the foot and ankle, has not been fully investigated.

Study performed at the Hospital Alemão Oswaldo Cruz, São Paulo, Brazil.

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Total ankle arthroplasty has become a viable alternative for treating advanced osteoarthritis, especially in countries with broader access to this technology. However, ankle arthrodesis remains the most widely used approach, with consolidation rates greater than 90% with current techniques<sup>(7)</sup>. Despite these results, pseudarthrosis can occur in 5% to 40% of cases, leading to instability and possible implant loosening<sup>(8,9)</sup>. Factors associated with nonunion include the fracture type, avascular necrosis, infection, comorbidities, smoking, and alcohol abuse<sup>(10)</sup>. In addition, the procedure performed, the postoperative alignment achieved, and the type of stabilization employed are critical factors that can directly impact bone consolidation and implant stability<sup>(8,9)</sup>.

Although previous studies have linked hypovitaminosis D to nonunion in orthopedic spine procedures, there is limited literature exploring the relationship between arthrodesis and serum vitamin D levels<sup>(11)</sup>.

Therefore, the objective of this article is to analyze whether vitamin D deficit is associated with pseudoarthrosis and implant loosening in ankle arthrodesis procedures.

# Methods Data source

The data used in this study was collected on February 6, 2025, from the TriNetX Network, which provides access to electronic medical records, including diagnoses, procedures, medications, laboratory results, and genomic information, for approximately 130 million patients in 84 health organizations. This network comprises Healthcare Organizations, including academic centers, specialized medical centers, and hospitals. In Brazil, the data are centralized in the DataLab for Innovation, Research, and Education of Oswaldo Cruz German Hospital in São Paulo, which operates as a TriNetX hub institution in Brazil. The platform provides aggregated and de-identified data and statistical summaries from participating health organizations worldwide. This ensures that platform users do not have access to any protected health information or personal data. Access to the data is available through the TriNetX search network at https://live.trinetx.com.

#### Study design

This retrospective observational study was conducted using data from the TriNetX Research Network. Inclusion criteria were: (1) patients submitted to ankle arthrodesis (tibiotarsal or tibiotalocalcaneal) open or arthroscopic; (2) Age  $\geq$  18 years; (3) at least one measurement of 25(OH)D recorded in the perioperative period; and (4) patients with outpatient follow-up for at least one year. Patients with a history of malignancy, liver disease, acute infections, or septic shock were excluded from the analysis. The 25(OH)D values were categorized into two groups: cohort 1-vitamin D deficiency ( $\leq$  20 ng/ml) and cohort 2-no deficiency (> 20 ng/ml)

Comorbidities were identified through the diagnostic codes of the International Classification of Diseases 10th revision (ICD-10)-(F17.2, I10, E08-E13, M19) and assessment of body mass index (BMI).

#### Outcomes evaluated

Incidence and prevalence of pseudoarthrosis and implant loosening/synthesis failure, within one year of follow-up of patients submitted to ankle arthrodesis. The outcomes were selected through the following ICD-10: M96.0 for pseudoarthrosis and T84.213, T84.21, and T84.22 for implant loosening/synthesis failure.

#### **Ethical considerations**

This retrospective study is exempt from Ethical approval. The revised data is a secondary analysis of existing data, does not involve intervention or interaction with humans, and is de-identified following the de-identification standard defined in Section § 164.514(a) of the Health Insurance Portability and Accountability Act (HIPAA). The process by which data is de-identified is attested through a formal determination by a qualified expert as defined in Section § 164.514(b)(1) of the HIPAA. This formal determination by a qualified expert was updated in December 2020.

#### **Statistical analysis**

Baseline characteristics of each group were compared using the chi-square test of independence for categorical variables and the paired Student's t-test for continuous variables. Demographic variations and comorbidities were extracted as covariates from electronic medical records, serving as potential confounding variables. Propensity score matching (1:1) was performed with logistic regression to control for age at the index date, sex, race, tobacco use, alcohol abuse, diabetes mellitus, BMI, and serum 25(OH)D levels. Propensity score was calculated using logistic regression implemented by the logistic regression function of the Scikit-learn package in Python version 3.7. After propensity score matching, measures of associations were used to calculate the odds ratio and risk difference, with 95% CI for the incidence of pseudarthrosis and implant loosening/synthesis failure. Kaplan-Meier analysis was performed to estimate cumulative probabilities of survival for each group one year from the index date using the Log-rank test. Statistical significance was established at p < 0.05 for all analyses.

#### Results

#### **Baseline characteristics**

Baseline characteristics of the cohort population are shown in Table 1. Patient selection (Figure 1) started with 3,767 patients, and after applying the exclusion criteria, the cohort included 306 patients aged  $\geq$  18 years. In cohort 1 (vitamin  $D \leq$  20 ng /ml), 92 patients with a mean age of 51.3 ± 13.7 were included. In cohort 2 (vitamin D cohort >20 ng/ml), 214 patients with a mean age of 58.7 ± 12.3 were included. Men were the majority in cohort 1, and women were the majority in cohort 2. The white race was more prevalent in both cohorts. Alcohol abuse (56.07%) and osteoarthritis (81.3%) were more present in cohort 2, while smoking (28.2%) was more reported in cohort 1. The percentage of BMI evaluated was similar, with a mean of 33.1  $\pm$  8.46 in cohort 1 and 33.1  $\pm$  7.41 in cohort 2. The mean 25(OH)D level was 14.6  $\pm$  4.59 in cohort 1 and 36.2  $\pm$  13.3 in cohort 2. Table 2 details the characteristics of cohort 1 after correspondence analysis, with 1:1 pairing.

 Table 1. Baseline characteristics of the cohort before propensity score pairing.

ICD-10	Demographic data	Vitamin D $\leq$ 20 n = 92			Vitamin D > 20 n = 214			p-value
		Mean ± SD	n	% cohort	Mean ± SD	n	% cohort	
	Age	51.3 ± 13.7	92	100%	58.7 ± 12.3	214	100%	< 0.0001
	Men		51	55.4%		90	42%	< 0.0034
	Women		37	40.2%		112	52.3%	< 0.0518
	Race							
	White		58	63%		173	80.8%	< 0.0009
	Black		23	25%		17	79.4%	< 0.0001
	Unknow		10	10.87%		18	84.1%	< 0.494
	Comorbidities							
F17.2	Tobacco use		26	28.2%		40	18.6%	< 0.620
F10	Alcohol abuse		10	10.8%		12	56.07%	< 0.102
M19	Osteoarthritis		57	61.9%		174	81.3%	< 0.0003
	BMI	33.1 ± 8.46	74	80.4%	33.1 ± 7.41	179	83.6%	< 0.4962
	25(OH)D	14.6 ± 4.59	73	79.3%	36.2 ± 13.3	179	83.6%	< 0.0001

ICD-10: International Classification of Diseases 10th revision; SD: Standard deviation; BMI: Body mass index; 25(OH)D: 25-hydroxyvitamin D.



Figure 1. Algorithm for selecting patients for the study.

ICD-10	Demographic data	Vitamin D≤20 n = 92			Vitamin D > 20 n = 214			p-value
		Mean ± SD	n	% cohort	Mean ± SD	n	% cohort	
	Age	53.3 ± 12.9	72	100%	53.1 ± 12.1	72	100%	< 0.941
	Men		35	48.6%		36	50%	< 0.8676
	Women		35	48.6%		36	50%	< 0.8676
	Race							
	White		49	68%		48	66.6%	< 0.859
	Black		14	19.4%		13	18%	< 0.83
	Unknow		10	13.8%		10	13.8%	< 10
	Comorbidities							
F17.2	Tobacco use		16	22.2%		15	20.8%	< 0.83
F10	Alcohol abuse		10	13.8%		10	13.8%	< 10
M19	Osteoarthritis		47	65.2%		46	63.8%	< 0.86
	BMI	33.1 ± 8.82	55	76.3%	33.6 ± 7.97	53	73.6%	< 0.74
	25(OH)D	14.9 ± 4.69	59	81.9%	31.8 ± 11.1	60	83.3%	< 0.0001

Table 2. Baseline characteristics of the cohort after propensity score matching 1:1.

ICD-10: International Classification of Diseases 10th revision; SD: Standard deviation; BMI: Body mass index; 25(OH)D: 25-hydroxyvitamin D.

The pairing process was responsible for pairing the baseline characteristics of the populations, such as age, sex, comorbidities, and vitamin D levels. After pairing, each cohort included 72 patients, and other similar data such as cohort 1 (men n = 35; woman n = 35); white race (cohort 1 (68%) vs. cohort 2 (66.6%)); smoking (cohort 1 (22.2%) vs. cohort 2 (20.8%)). The mean and standard deviation of serum 25(OH)D levels were the only characteristics that remained statistically significant after pairing the cohorts.

The incidence of pseudoarthrosis and implant loosening in cohort 1 was 21.1% and 10.86%, respectively. While the prevalence in the studied period was 27.7% and 10.86% (Table 3).

#### Outcomes

For the pseudarthrosis outcome, there was no significance regarding the difference in risk between groups: -1.919% (95% CI: -16.153% to 12.315%, p = 0.7912); The probability of pseudarthrosis between the cohorts was similar: Odds Ratio 0.878 (95% CI: 0.333 - 2.309) (Table 4). Regarding the analysis of pseudoarthrosis-free survival, the associated statistical analysis ( $\chi^2$  = 0.019, p = 0.891), by the Log-rank test, indicated that there was no statistically significant difference between the survival curves (Figure 2).

For the implant loosening/synthesis failure outcome, there was no significance in relation to the difference in risk between the cohorts: 0.207% (95% CI: -11.463% to 11.877%), with p = 0.9723; The probability of pseudarthrosis between the cohorts was similar: Odds atio 1.017 (95% CI: 0.394 - 2.623) (Table 5). Regarding the analysis of pseudoarthrosis-free survival, the associated statistical analysis ( $\chi^2$  = 0.372, p = 0.54), by the Log-rank test, indicated that there was no statistically significant difference between the survival curves (Figure 3).

**Table 3.** Table of incidence and prevalence of pseudoarthrosis and implant loosening in patients with vitamin  $D \le 20$  ng/ml.

	Incidence	Prevalence
Pseudoarthrosis	21.1%	27.17%
Implant loosening	10.86%	10.86%

**Table 4.** Measures of association for pseudoarthrosis outcomebefore propensity score pairing.

		Cohort patients		Patie re:	nts with sults	Risk		
1	1 Vitamin D ≤ 20 ng/ml		59		≤10*		16.94%	
2	2 Vitamin D > 20 ng/ml		53		≤10*		18.86%	
Ris dif	k ference	IC 95%	z	p	Risk ratio	IC 95%	Odds Ratio	IC 95%
-1.9	919%	(-16.15%; 12.31%)	- 0.265	0.7912	0.898	(0.406; 1.988)	0.878	(0.333; 2.309)

\*13 patients in cohort 1 and 19 patients in cohort 2 were excluded from the results because they had outcomes outside the time frame. To protect patient privacy, numbers are rounded up to 10 This may affect the results, especially for small cohorts and infrequent outcomes. C1: Confidence interval

# Discussion

In this retrospective cohort study using the international TriNetX database, reduced vitamin D levels ( $\leq$  20 ng/mL) were observed but were not significantly associated with an increased risk of pseudarthrosis or implant loosening within one year. These findings challenge the widely accepted



Figure 2. Kaplan-Meier survival curve for pseudoarthrosis outcome considering serum vitamin D level.

 Table 5. Measures of association for implant loosening outcome after propensity score pairing.

		Cohort patients		Patier res	nts with sults	Risk		
1	Vitamin D ≤ 20 ng/ml		69		≤10*		14,49%	
2	2 Vitamin D > 20 ng/ml		70		≤10*		14,28%	
Ris dif	sk ference	IC 95%	z	р	Risk ratio	IC 95%	Odds Ratio	IC 95%
-0	.207%	(-11.46%; 11.87%)	0.035	0.9723	1.1014	(0.451; 2.283)	1.017	(0.394; 2.623)

\*10 patients in cohort 1 and 10 patients in cohort 2 were excluded from the results because they had outcomes outside the time frame. To protect patient privacy, numbers are rounded up to 10 This may affect the results, especially for small cohorts and infrequent outcomes. CI: Confidence interval.



Figure 3. Kaplan-Meier survival curve for implant loosening outcome considering serum vitamin D level.

assumption that vitamin D deficiency alone is an essential factor in bone remodeling and, consequently, the stability of ankle arthrodesis implants<sup>(12)</sup>.

The importance of this analysis lies in the need to differentiate purely metabolic and biochemical factors from biomechanical and structural factors<sup>(13)</sup>, which can exert a greater influence on implant stability and bone healing in orthopedic surgeries<sup>(14)</sup>.

In our study, the lack of a statistically significant association of the ratio and difference in risks of low 25(OH)D levels with pseudarthrosis differs from the systematic review by Christianson et al.<sup>(15)</sup> and the study by Gorter et al.<sup>(16)</sup>, which correlate hypovitaminosis D with the difficulty of consolidation in orthopedic procedures. However, it agrees with the case-control by Moore et al.<sup>(17)</sup> and the observational cohort by Hendrickson et al.<sup>(18)</sup>, in which there was no such correlation. In the literature, Igarashi et al.<sup>(19)</sup> reported a case of pediatric femoral fracture that progressed to pseudoarthrosis associated with vitamin D and K deficiency, suggesting that multiple metabolic factors may influence bone consolidation failure. However, this relationship has not been consistently reproduced in adult populations, in which factors such as biomechanical instability, inadequate axial load, and smoking have demonstrated a more direct impact on consolidation failure<sup>(20)</sup>. In fact, controversies are evident, and even more elaborate studies emphasize the need for new scientific evidence.

Almost an intrinsic relationship to pseudoarthrosis, the implant loosening is conditioned, although associated with several factors, to a biomechanical synthesis stability<sup>(21,22)</sup>. Some authors suggest that vitamin D deficiency could contribute to a chronic inflammatory environment, favoring periprosthetic osteolysis and, consequently, implant failure<sup>(23)</sup>. However, Maier et al.<sup>(24)</sup> demonstrated that reduced vitamin D levels were not an independent predictor of periprosthetic infection or implant loosening, suggesting that biomechanical and systemic factors may be more relevant to this process.

In contrast, studies such as that of Peersman et al.<sup>(25)</sup> hypothesize that elevated vitamin D levels could paradoxically increase bone resorption at the implant-bone interface due to local macrophage activation and periprosthetic inflammation. This mechanism could justify the absence of a linear relationship between hypovitaminosis D and implant failure, reinforcing that vitamin D supplementation does not always translate into direct clinical benefits.

Vitamin D supplementation has been widely recommended in orthopedic practice to optimize bone formation and prevent failures in reconstructive surgeries<sup>(26-28)</sup>. However, clinical evidence on its direct impact on pseudoarthrosis and implant failure is still limited and is further investigated in the context of dental implants<sup>(29)</sup>. Therefore, although there is evidence that severe vitamin D deficiency can affect bone formation, current data suggest that its replacement should be considered a complementary metabolic support, and not an isolated therapeutic strategy to prevent pseudoarthrosis or implant failure<sup>(30)</sup>.

Thus, the evaluation of the orthopedic patient should be multifactorial, prioritizing bone quality, control of comorbidities, and surgical technique, without attributing exclusively to hypovitaminosis D the central role in implant failure.

Strengths of this study include the well-characterized cohort of patients with ankle arthrodesis and perioperative vitamin D levels. In addition to the comprehensive demographic and clinical data, the follow-up period. However, the study has several limitations. First, its observational design does not allow for the complete exclusion of residual or unmeasured confounding factors. In addition to the difficulty in establishing causal relationships or inferring direct causality. This issue can be addressed in future studies through randomization analyses. Second, searching for procedure codes and using ICD-10 codes can introduce inaccuracies, potentially leading to incorrect classification. Third, most TriNetX data is from structured electronic health records, often lacking detailed information about the selected endpoints. Fourth, the study population consists mostly of individuals from developed countries, which may limit the generalization of the findings to other populations with different demographic characteristics. Finally, data on multifactorial factors were limited. Despite these limitations, the study provides a valuable basis for future research on optimizing orthopedic surgeries regarding serum 25-(OH)D levels.

#### Conclusion

Vitamin D deficiency can influence bone formation, but there is no conclusive direct evidence that it increases the risk of pseudarthrosis or implant loosening in the short term. Preoperative supplementation may benefit patients with severe vitamin D deficiency, but its clinical impact still needs further investigation in randomized clinical trials.

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