TITLE:

VITAMIN D AND FOOT AND ANKLE TRAUMA. AN INDIVIDUAL OR SOCIETAL PROBLEM?

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ABSTRACT:

Background:

Vitamin D deficiency is a worldwide health concern. Hypovitaminosis D may adversely affect recovery from bone injury. We aimed to perform an audit of the Vitamin D status of patients in three centres in the United Kingdom presenting with foot and ankle osseous damage.

Methods:

Serum 25-hydroxyvitamin-D (vitamin D) levels were obtained in 308 patients presenting to Orthopaedic Units with imaging confirmed foot and ankle bony trauma. Variables including age, gender, ethnicity, location, season, month, anatomical location and type of bone injury were recorded.

Results:

308 patients were included from three different centres. 66.6% were female. The average age was 47.7 (median 50, range 10 to 85). 170 patients were treated in Northampton, 80 in Chester and 58 in Leicester. The mean hydroxyvitamin-D levels were 52.0 nmol/L (SD 28.5; range 12.2 to 168.4) and the median 42.3 nmol/L. 18.8% were grossly deficient, 23.7% deficient, 34.7% insufficient and 22.7% within normal range. 351 separate bone injuries were identified of which 104 were categorised as stress reactions, 134 as stress fractures, 105 as fractures and 8 as established non-unions. Age, gender, anatomical location and fracture type did not statistically affect vitamin D levels. Ethnicity did affect Vitamin D levels: non-Caucasians mean levels were 32.4 n/mols/L compared to Caucasian levels of 53.2 nmol/L p=0.0026). The cohorts from Northampton and Leicester were compared to the elective foot and ankle surgical patient groups who underwent pre-operative Vitamin D screening

during the period of observation. The analysis revealed similarly high proportions of patients with low levels of circulating Vitamin D levels.

Conclusion:

Only 18.8% of our trauma patients had a normal Vitamin D level and 22.7% were grossly deficient. Ethnicity did significantly affect Vitamin D results. Patient age, gender, anatomical location and injury type did not statistically affect vitamin D levels. The findings in two of the centres' cohorts closely mirrors that of their elective foot and ankle surgical patients. This suggests that hypovitaminosis D is a problem of society in general rather than specific to specific foot and ankle injury patterns or particular patient groups sustaining trauma.

Level of evidence: 2b

Keywords:

Vitamin D ; Stress fracture ; Epidemiology ; Foot ; hypovitaminosis

INTRODUCTION:

The importance of Vitamin D in maintaining calcium homeostasis has long been recognised. Consequently, its pivotal role in bone maintenance and repair processes is believed to be important for optimal healing of traumatised bones.

However, widespread hypovitaminosis D has been reported affecting industrialised as well as third-world societies.[23] Within the United Kingdom, 7.5% of under 3 year olds, 24.4% of females aged 11 to 18 years old, and 16.9% of males and 24.1% of females over 65 years old have vitamin D levels lower than 25nmol/L rendering them grossly deficient.[5]

The authors' previous work has demonstrated that 21.7% of patients presenting to their clinics for elective foot and ankle surgery had levels below 30nmol/L.[3]

As well as a role in promoting healthy bones, vitamin D is important in preventing muscle atrophy, weakness, joint pains and nerve dysfunction. These are all important elements in promoting rehabilitation from injury.[2,7,40,41,49] Therefore, it is accepted that patients presenting to our Orthopaedic Clinics will be drawn from a population where a sizeable minority will be deficient in Vitamin D. However, does the cohort presenting with bony foot and ankle trauma represent a sub-group with a greater tendency to hypovitaminosis D? Previous studies on fracture patients and Vitamin D levels have suggested that this is the case.[9,33,48] Without being able to compare with normal populations from the same locations, such conclusions are difficult to draw. Smith *et al* did compare their foot and ankle fractures with a small group of ankle sprain patients: they found the fracture group to have significantly lower Vitamin D levels than the ligament group.[47]

Our study aimed to review the Vitamin D status of patients presenting to three different Orthopaedic units in England with foot and ankle bone trauma. As such we have been able to assemble the largest cohort to date on this subject. We examined whether different fracture types and locations were associated with altered Vitamin D profiles. Additionally, we reviewed whether patient age, gender or ethnicity and time of the year for injury were associated with different Vitamin D levels. Finally, two of the three centres have contemporary data of the Vitamin D status of patients admitted for elective foot and ankle surgery to allow comparison with the trauma groups.

METHODS:

Subjects:

308 patients with imaging evidence of osseous foot and ankle trauma who attended the Orthopaedic Clinics of the three senior clinicians (WJR: Northampton; PEA: Leicester; EVW: Chester) had their vitamin D blood levels (serum 25-hydroxyvitamin D (25[OH])D) measured as a routine part of their bone health assessment. The importance of vitamin D and bone health was discussed with the patients prior to testing. The results of the vitamin D measurement were reviewed with the patients at follow-up consultations and advice given to those deemed deficient relating to the importance of vitamin D supplementation.

Patient Demographics:

Routine data was recorded on each patient including age, sex, ethnicity, date of blood sampling, anatomical location and type of bone injury.

Vitamin D levels:

The literature varies in agreement upon a classification for normality and deficiency of serum vitamin D levels. In keeping with previous authors and our own previous publication[3], we defined normal as >75 nmol/L; insufficiency as 50 to 75 nmol/L; deficiency as less than 31 to 50 nmol/L; and grossly deficient as less than 30 nmol/L.

Serum Analysis:

Samples were analysed at the Pathology Departments of Northampton General Hospital (NGH), the Countess of Chester Hospital (CCH) and Leicester General Hospital (LGH). An assay of the serum 25-hydroxyvitamin-D levels were taken, and the results fed back to patient and surgeon. The NGH laboratories uses the Roche Cobas e 602 machine to perform an electrochemiluminescence binding assay for serum 25-hydroxyvitamin-D levels. The CCH laboratories use the Beckman Coulter UNICEL DxI 800 ACCESS immunoassay machine. The Leicester biochemistry laboratory uses the ADVIA Centaur XPT machine to perform immunoassays for serum 25-hydroxyvitamin-D levels.

Variables:

Bone trauma was described in two ways: firstly, according to anatomical location. For some patients more than one bone was involved. In these cases, each bone was counted separately and a Vitamin D level ascribed to each damaged bone.

Secondly, the type of injury was recorded:

- Stress reaction: This was defined as a patient presenting with pain following trauma and MRI evidence of a stress reaction within one or more bones. Patients with associated significant soft-tissue injury and with an associated bone reaction, e.g. an ankle inversion injury causing lateral ligament injury and a talus bone bruise were excluded.

- Stress fracture
- Fracture
- Non-union: This was defined as a patient presenting for the first time to a clinic with an established non-union, e.g. a sesamoid non-union.

Age was identified at time of blood test. The sub-groups of age used for analysis were less than 30, 30 to 49, 50 to 69, and 70 or older. Ethnicity was defined as Caucasian, Asian and Afro-Caribbean. Because of the low number of non-Caucasian patients within the overall sample, the Asian and Afro-Caribbean patients were summated for comparison with the Caucasian cohort (Table 3). Seasons were defined as Winter (January, February, March), Spring (April, May, June), Summer (July, August, September) and Autumn (October, November, December).

Statistical Analysis:

The serum 25-hydroxyvitamin D assay results for the 308 patients were subjected to statistical analysis. The results were analysed separately for each Orthopaedic Unit, fracture type and location, and all together. The mean, median and standard deviation were determined, and the proportion of patients categorised as normal, insufficient, deficient, or grossly deficient were also determined.

Univariate and multivariate logistic regression analysis was used to assess each independent risk factor. Vitamin D levels were used as the dependent variable. Where independent variable was continuous Pearson's correlation was utilised. Where independent variables were categorical either paired t-test or one-way ANOVA were used. Bonferroni comparison was used where appropriate. A significance level was set at $p \leq 0.05$. Statistical analysis was performed using STATA version 14.2 (StataCorp, TX, USA).

RESULTS:

Patient Demographics:

308 patients were included over the analysis. 66.6% were female. The mean age was 47.7 (median 50, range 10-85). 170 patients were treated in Northampton, 80 in Chester and 58 in Leicester. The demographic, ethnicity and fracture characteristics between Northampton, Chester and Leicester cohorts are shown in Tables 1, 2 and 3.

Vitamin D serum levels:

The mean serum 25-hydroxyvitamin-D levels for the overall patient group was 52.0 nmol/L (SD 28.5; range 12.2 to 168.4) and the median 42.3 nmol/L. By category 18.8 % were grossly deficient, 23.7 % deficient, 34.7 % insufficient and 22.7 % within normal range (Table 1).

Fracture location and type:

From the 308 patients, 32 patients had more than one recognised site of bone injury. A total of 351 separate bone injuries were identified. Table 2 demonstrates the anatomical distribution of the bone injuries and the fracture type.

Sub-group analysis:

The various sub-groups were analysed for statistical differences. The results are shown in Table 3.

Age:

Table 3 highlights the differences between age ranges (one-way ANOVA). No statistical difference was found between age groups. There was no correlation with age and vitamin D level (r=-0.054, Pearson's correlation).

Gender:

Gender did not statistically affect vitamin D levels (p=0.104, *t*-test). This was the case for all locations and the patients overall.

Ethnicity:

Vitamin D levels were statistically higher for Caucasians with a mean of 53.2 nmol/L (SD 28.7, n=290) compared to 32.4 nmol/L (SD 16.4, n=18) for non-Caucasian patients (p=0.0026, *t*-test).

Geographic location:

Mean vitamin D levels were 57.8 (SD 29.9) for 170 patients based in Northampton, 46.0 (SD 22.8) for the 80 Chester patients, and 44.3 (SD 27.7) for 58 patients based in Leicester. Northampton had a statistically significant (p<0.05) higher vitamin D level over Chester and Leicester.

Seasonal variation:

The values for each season are shown in Table 3. As anticipated the summer values were highest and the winter levels the lowest. Summer months had a statistically significant higher vitamin D level over Winter and Spring months. Autumn months had a higher vitamin D level over Winter (p<0.05).

Comparison between Foot Ankle Trauma and Elective Foot and Ankle Patients:

The data of the demographics and Vitamin D levels of 577 consecutive patients admitted to the Northampton and Leicester units contemporaneously to the treatment of the trauma patients under analysis was available for comparison. The results are depicted in Figure 4. There was no statistically significant difference in terms of Vitamin D levels between the elective and trauma groups including comparisons based upon sex, age, ethnicity and season. The proportions of patients falling within the four levels of Vitamin D status, i.e. normal, insufficient, deficient, and grossly deficient, were similar.

DISCUSSION:

The global impact of widespread vitamin D deficiency and its influence on numerous disease processes has received attention from governmental agencies as well as the clinical community. Within Europe the cost of vitamin D deficiency has calculated to be in the region of €187 billion/year.[20] A similar study calculated that $12.5 ± 6 billion could be saved in annual economic burden of disease in Canada by increasing all citizens serum 25-hydroxyvitamin-D levels to greater than 100 nmol/L.[21] It has been claimed that doubling world mean vitamin D levels could be the single most cost-effective way to reduce global mortality.[19] However, Manson *et al* question the validity of claims of a global pandemic and cite misapplication of the RDA as a cut-off point to define inadequacy.[34] They argue against whole population screening & treatment and advocate targeted Vitamin D assessment and treatment in at risk groups.[34]

Although experimental evidence in animals has demonstrated the benefits of Vitamin D supplementation in fracture healing,[13,16,38] the evidence is not so clear in humans. In a systematic review of the literature, Gorter *et al* reported that having reviewed 135 publications,[18] Vitamin D appeared to have a role in fracture healing but that the data was inconsistent to explain how. Additionally, the knowledge of the effects of both hypovitaminosis and supplementation was scarce and inconclusive.[18]

Low Vitamin D levels are particularly prevalent in Orthopaedic Trauma patients: a study of 899 trauma patients found the overall rate of Vitamin D deficiency/insufficiency to be 77% with 39% being deficient (≤20ng/ml).[25] A small cohort of post-menopausal women with hip fractures were reported as showing a 50% incidence of levels <30 nmol/L.[33] Two North American papers on foot and ankle fractures and Vitamin D levels warrant further analysis.[35,47] Miller *et al* reported on 124 stress fractures, of whom 53 had Vitamin D levels measured.[35] The mean level was 78.5 +/- 36.8 nmol/L and 53% of the patients had levels <75nmol/L. Smith *et al* reported on 75 patients with low energy foot & ankle fractures.[47] They found a mean Vitamin D level of 78.2 +/- 29.5 nmol/L and 47% of patients had levels <75 nmol/L. The authors found a relationship between low Vitamin D levels and smoking, obesity and medical co-morbidities associated with hypovitaminosis D such as, chronic renal insufficiency and gastrointestinal absorption irregularities. Neither paper analysed the relationship of anatomical location or fracture type any further. Both American papers report substantially higher average Vitamin D levels in their cohorts than in this United Kingdon (UK) based paper. This is a similar trend to our previous paper on elective foot and ankle surgery patients where only 18% of patients had levels greater than 75 nmol/L compared to Bogunovic's New York elective patients where 66% had levels greater that 75 nmol/L.[3,8] The higher latitudes of the locations from which the UK cohort was recruited is possibly influential, with an estimated level of sunshine hours per year only 60% of New York.[10] Routine food fortification with Vitamin D may also explain this difference.[11] A statistically significant seasonal variation in injury pattern was seen by Williams *et al*,[50] who looked at Vitamin D levels in patients presenting with low energy foot and ankle sprains and metatarsal fractures. Both groups had a similar proportion affected by insufficient Vitamin D levels (66% in fracture group, 71% in sprain group, p=0.81) but there were more fractures seen in the winter and sprains in the summer (p=0.02).[50] A study of 5th metatarsal fractures from Wales UK, also shows similar findings, with a low mean Vitamin D level of 43.7 nmol/l (20.2 to 124.0) in 40 patients.[12] Although there was a trend towards higher Vitamin D levels in the summer, this did not reach significance (p=0.06).[12]

Low vitamin D levels have been associated with delayed healing of fractures and for elective fusions. Brinker found two-thirds of patients with unexplained non-unions following fractures had hypovitaminosis D.[9] Patton recommended patients with non-unions should be screened for low Vitamin D levels.[39] Moore *et al* found that Vitamin D deficiency or insufficiency was associated were 8.1 times more likely to experience a non-union after elective foot and ankle reconstruction.[36] Most recently, in a retrospective study of 37 military recruits with stress fractures, an association between the time taken to recover and Vitamin D level was demonstrated. Those with levels >50nmol/L recovering in a significantly shorter time.[44]

This raises the question of the efficacy of supplementation, on bony union, in those with hypovitaminosis D. A single, high dose, of Vitamin D (100 000 IU) in adults with long bone fractures and Vitamin D insufficiency, was not shown to have an effect on the non-union rate, compared to a control group (4% in both groups).[22] Other studies have looked at the effect of Vitamin D alone or in combination with calcium or bisphosphonates on bone mineral density.[4,15,43] However, exploration of this is beyond the scope of this paper.

Despite analysing the foot and ankle injuries according to anatomical location, we could not identify any specific sub-group presenting with either high or low Vitamin D levels. The pattern of Vitamin D status was similar to a contemporaneous cohort of elective foot and ankle patients in two of the units studied.[3] The foot and ankle is a region of the body particularly prone to stress fractures. Moreover, certain groups are more likely to develop such injuries including those in the military and track and field athletes. In the military, stress fractures were reported in between 0.2% to 5.2% of male recruits and 1.6% to 30% in females.[1,29,31,32,42,46] In track and field athletes stress fracture rates between 10 to 30% have been reported.[6,28,30,42] Lappe *et al* reported a 21% drop in stress fractures in female military recruits during a period of 24 months of calcium and vitamin D supplementation.[32] The combination of Vitamin D and Calcium has also been shown to reduce the risk of fracture in pooled analysis of 68500 patients, but there was no effect from taking just Vitamin D alone.[14]

Lack of dietary Vitamin D intake has been identified as a risk factor for stress fractures in athletes.[17] Giffin *et al* identified inadequate Vitamin D intake in both male & female runners compared to runners without fractures (38.8% and 45.2% respectively).[17] Regimens for Vitamin D supplementation within the normal population and for those with recognised hypovitaminosis have been published at home and abroad.[24,27] Current guidelines in the United Kingdom were recently updated by the Scientific Advisory Committee on Nutrition (July 2016). The Committee has recommended that everyone over the age of 4 years old should have an RNI (Reference Nutrient Intake) of Vitamin D of 400 iu/day throughout the year.[45] Several sporting organisations within the United Kingdom have issued dietary guidelines for Vitamin D supplementation in health and following fractures.[26,37] The dietary and supplementation advice offered to our patients with foot and ankle fractures follows the advice of the English Cricket Board working party of which one of the authors (WJR) was a contributor.[26] Patients with levels <35nmol/L should be placed upon 50,000iu/week for six weeks and for levels between 35-75nmol/L require 50,000iu/week for three weeks. After this period, blood levels should be re-checked to assess rising vitamin D levels and further advice accordingly. For those over 75nmol/L, a supplement or 1000iu/day over the winter months is recommended. Our aim was to bring levels to at least 75nmol/L for patients recovering from fractures.

Similar to previous reports, this study confirms that our foot and ankle trauma group have an overall low Vitamin D profile. Four out of five patients were demonstrated to have sub-optimal levels of serum Vitamin D. However, the Vitamin D distribution is like a previously studied large group of foot and ankle elective patients.[2] This suggest that either patients presenting with foot and ankle problems, whether elective or trauma, tend towards low Vitamin D levels or, more probably, the populations which the senior authors serve have generally low circulating levels. What remains to be answered is whether these low societal levels represent a significant risk factor for sustaining foot and ankle trauma? Would public health measures, such as education and guidelines, to raise vitamin levels through sunlight exposure and diet reduce trauma risk? Our analysis confirmed what previous work has reported,[2] that serum Vitamin D levels are highest during the summer months.

Age and sex do not appear to influence levels in our cohort, but non-Caucasians do have lower levels of Vitamin D.

The authors acknowledge some limitations within this report. Firstly, the specimens were analysed in three separate local biochemistry departments, which can lead to some variation in results. The audit did not set out to analyse the effects of hypovitaminosis D on subsequent delayed and non-union rates in these bone injuries. Vitamin D deficient patients were advised of the findings and remedial advice given during the recovery period. The study attempted to identify the scale of the problem in this cohort and to seek indicators of potential high-risk groups and fracture types: this would help to guide advice to our patients. We did not analyse the patients taking vitamin D supplementation pre-injury. The number was believed to be small, the dosage taken and compliance was variable: meaningful analysis was deemed impossible. Additionally, we did not record such risk factors for hypovitaminosis D such as obesity, cigarette smoking and co-morbidities.

Conclusions:

This study confirms that low levels of Vitamin D are found in the majority of patients sustaining foot and ankle trauma. Less than one-fifth of patients had adequate Vitamin D levels. Vitamin D levels were lowest in non-Caucasian patients. However, the analysis did not reveal any specific fracture type or anatomical location most at risk of hypovitaminosis. Similarly, the Vitamin D profile is similar to an elective foot and ankle surgical group. Hypovitaminosis is a societal problem, which is confirmed by our study results.

REFERENCES

1. Almeida SA, Williams KM, Shaffer RA, Brodine SK. Epidemiological patterns of musculoskeletal injuries and physical training. *Med Sci Sports Exerc*. 1999;31(8):1176-1182.

2. Al-Said YA, Al-Rached HS, Al-Qahtani HA, Jan MMS. Severe proximal myopathy with remarkable recovery after vitamin D treatment. *Can J Neurol Sci J Can Sci Neurol*. 2009;36(3):336-339.

3. Aujla RS, Allen PE, Ribbans WJ. Vitamin D levels in 577 consecutive elective foot & ankle surgery patients. *Foot Ankle Surg Off J Eur Soc Foot Ankle Surg*. December 2017. doi:10.1016/j.fas.2017.12.007.

4. Aydoğan NH, Özel İ, İltar S, Kara T, Özmeriç A, Alemdaroğlu KB. The effect of vitamin D and bisphosphonate on fracture healing: An experimental study. *J Clin Orthop Trauma*. 2016;7(2):90-94. doi:10.1016/j.jcot.2016.01.003.

5. Bates B, Lennox A, Prentice A, et al. National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009-2011/2012): A survey carried out on behalf of Public Health England and the Food Standards Agency. 2014.

6. Bennell KL, Malcolm SA, Thomas SA, Wark JD, Brukner PD. The incidence and distribution of stress fractures in competitive track and field athletes. A twelve-month prospective study. *Am J Sports Med*. 1996;24(2):211-217. doi:10.1177/036354659602400217.

7. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized

Clinical Trial. *JAMA Intern Med*. 2016;176(2):175-183. doi:10.1001/jamainternmed.2015.7148.

8. Bogunovic L, Kim AD, Beamer BS, Nguyen J, Lane JM. Hypovitaminosis D in patients scheduled to undergo orthopaedic surgery: a single-center analysis. *J Bone Joint Surg Am*. 2010;92(13):2300-2304. doi:10.2106/JBJS.I.01231.

9. Brinker MR, O'Connor DP, Monla YT, Earthman TP. Metabolic and endocrine abnormalities in patients with nonunions. *J Orthop Trauma*. 2007;21(8):557-570. doi:10.1097/BOT.0b013e31814d4dc6.

10. Bruyere O, Decock C, Delhez M, Collette J, Reginster J-Y. Highest prevalence of vitamin D inadequacy in institutionalized women compared with noninstitutionalized women: a case-control study. *Womens Health Lond Engl*. 2009;5(1):49-54. doi:10.2217/17455057.5.1.49.

11. Cashman KD, Muldowney S, McNulty B, et al. Vitamin D status of Irish adults: findings from the National Adult Nutrition Survey. *Br J Nutr*. 2013;109(7):1248-1256. doi:10.1017/S0007114512003212.

12. Clutton J, Perera A. Vitamin D insufficiency and deficiency in patients with fractures of the fifth metatarsal. *Foot Edinb Scotl*. 2016;27:50-52. doi:10.1016/j.foot.2015.08.005.

13. Copp DH, Greenberg DM. Studies on Bone Fracture HealingI. Effect of Vitamins A and D. *J Nutr*. 1945;29(4):261-267. doi:10.1093/jn/29.4.261.

14. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ*. 2010;340:b5463. doi:10.1136/bmj.b5463.

15. Doetsch AM, Faber J, Lynnerup N, Wätjen I, Bliddal H, Danneskiold-Samsøe B. The effect of calcium and vitamin D3 supplementation on the healing of the proximal humerus fracture: a randomized placebo-controlled study. *Calcif Tissue Int*. 2004;75(3):183-188. doi:10.1007/s00223-004-0167-0.

16. Fu L, Tang T, Miao Y, Hao Y, Dai K. Effect of 1,25-dihydroxy vitamin D3 on fracture healing and bone remodeling in ovariectomized rat femora. *Bone*. 2009;44(5):893-898. doi:10.1016/j.bone.2009.01.378.

17. Giffin KL, Knight KB, Bass MA, Valliant MW. Predisposing Risk Factors and Stress Fractures in Division I Cross Country Runners. *J Strength Cond Res*. November 2017. doi:10.1519/JSC.0000000000002408.

18. Gorter EA, Hamdy NAT, Appelman-Dijkstra NM, Schipper IB. The role of vitamin D in human fracture healing: a systematic review of the literature. *Bone*. 2014;64:288-297. doi:10.1016/j.bone.2014.04.026.

19. Grant WB. An estimate of the global reduction in mortality rates through doubling vitamin D levels. *Eur J Clin Nutr*. 2011;65(9):1016-1026. doi:10.1038/ejcn.2011.68.

20. Grant WB, Cross HS, Garland CF, et al. Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. *Prog Biophys Mol Biol*. 2009;99(2-3):104-113. doi:10.1016/j.pbiomolbio.2009.02.003.

21. Grant WB, Whiting SJ, Schwalfenberg GK, Genuis SJ, Kimball SM. Estimated economic benefit of increasing 25-hydroxyvitamin D concentrations of Canadians to or above 100 nmol/L. *Dermatoendocrinol*. 2016;8(1):e1248324. doi:10.1080/19381980.2016.1248324.

22. Haines N, Kempton LB, Seymour RB, et al. The effect of a single early high-dose vitamin D supplement on fracture union in patients with hypovitaminosis D: a prospective randomised trial. *Bone Jt J*. 2017;99-B(11):1520-1525. doi:10.1302/0301-620X.99B11.BJJ-2017-0271.R1.

23. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266-281. doi:10.1056/NEJMra070553.

24. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930. doi:10.1210/jc.2011-0385.

25. Hood MA, Murtha YM, Della Rocca GJ, Stannard JP, Volgas DA, Crist BD. Prevalence of Low Vitamin D Levels in Patients With Orthopedic Trauma. *Am J Orthop Belle Mead NJ*. 2016;45(7):E522-E526.

26. Houghton J, Ribbans W, Wedatilake T, Peirce N, Rosimus C. Vitamin D Guidelines. 2017.

27. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. (Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds.). Washington (DC): National Academies Press (US); 2011. http://www.ncbi.nlm.nih.gov/books/NBK56070/.

28. Johnson AW, Weiss CB, Wheeler DL. Stress fractures of the femoral shaft in athletes--more common than expected. A new clinical test. *Am J Sports Med*. 1994;22(2):248-256. doi:10.1177/036354659402200216.

29. Jones BH, Cowan DN, Tomlinson JP, Robinson JR, Polly DW, Frykman PN. Epidemiology of injuries associated with physical training among young men in the army. *Med Sci Sports Exerc*. 1993;25(2):197-203.

30. Jones BH, Thacker SB, Gilchrist J, Kimsey CD, Sosin DM. Prevention of lower extremity stress fractures in athletes and soldiers: a systematic review. *Epidemiol Rev*. 2002;24(2):228-247.

31. Kelly EW, Jonson SR, Cohen ME, Shaffer R. Stress fractures of the pelvis in female navy recruits: an analysis of possible mechanisms of injury. *Mil Med*. 2000;165(2):142-146.

32. Lappe J, Cullen D, Haynatzki G, Recker R, Ahlf R, Thompson K. Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. *J Bone Miner Res Off J Am Soc Bone Miner Res*. 2008;23(5):741-749. doi:10.1359/jbmr.080102.

33. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. *JAMA*. 1999;281(16):1505-1511.

34. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D Deficiency - Is There Really a Pandemic? *N Engl J Med*. 2016;375(19):1817-1820. doi:10.1056/NEJMp1608005.

35. Miller JR, Dunn KW, Ciliberti LJ, Patel RD, Swanson BA. Association of Vitamin D With Stress Fractures: A Retrospective Cohort Study. *J Foot Ankle Surg Off Publ Am Coll Foot Ankle Surg*. 2016;55(1):117-120. doi:10.1053/j.jfas.2015.08.002.

36. Moore KR, Howell MA, Saltrick KR, Catanzariti AR. Risk Factors Associated With Nonunion After Elective Foot and Ankle Reconstruction: A Case-Control Study. *J Foot Ankle Surg Off Publ Am Coll Foot Ankle Surg*. 2017;56(3):457-462. doi:10.1053/j.jfas.2017.01.011.

37. Newton J, Lewis N. EIS Position Stand on the testing and interpretation of Vitamin D levels and prescription of Vitamin D supplements in Elite Sport. Version 2. June 2013.

38. Ömeroĝlu H, Ates Y, Akkuş O, Korkusuz F. Biomechanical analysis of the effects of single high-dose vitamin D3 on fracture healing in a healthy rabbit model. *Arch Orthop Trauma Surg*. 1997;116(5):271-274. doi:10.1007/BF00390051.

39. Patton CM, Powell AP, Patel AA. Vitamin D in orthopaedics. *J Am Acad Orthop Surg*. 2012;20(3):123-129. doi:10.5435/JAAOS-20-03-123.

40. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc*. 2003;78(12):1463-1470. doi:10.4065/78.12.1463.

41. Prineas JW, Mason AS, Henson RA. MYOPATHY IN METABOLIC BONE DISEASE. *Br Med J*. 1965;1(5441):1034-1036.

42. Rauh MJ, Macera CA, Trone DW, Shaffer RA, Brodine SK. Epidemiology of stress fracture and lower-extremity overuse injury in female recruits. *Med Sci Sports Exerc*. 2006;38(9):1571-1577. doi:10.1249/01.mss.0000227543.51293.9d.

43. Reid IR. Vitamin D Effect on Bone Mineral Density and Fractures. *Endocrinol Metab Clin North Am*. 2017;46(4):935-945. doi:10.1016/j.ecl.2017.07.005.

44. Richards T, Wright C. British Army recruits with low serum vitamin D take longer to recover from stress fractures. *J R Army Med Corps*. October 2018. doi:10.1136/jramc-2018-000983.

45. Scientific Committee on Nutrition (SACN): Vitamin D and Health. July 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf.

46. Shaffer RA, Rauh MJ, Brodine SK, Trone DW, Macera CA. Predictors of stress fracture susceptibility in young female recruits. *Am J Sports Med*. 2006;34(1):108-115. doi:10.1177/0363546505278703.

47. Smith JT, Halim K, Palms DA, Okike K, Bluman EM, Chiodo CP. Prevalence of vitamin D deficiency in patients with foot and ankle injuries. *Foot Ankle Int*. 2014;35(1):8-13. doi:10.1177/1071100713509240.

48. Smith LM, Gallagher JC. Dietary Vitamin D Intake for the Elderly Population: Update on the Recommended Dietary Allowance for Vitamin D. *Endocrinol Metab Clin North Am*. 2017;46(4):871-884. doi:10.1016/j.ecl.2017.07.003.

49. Tague SE, Clarke GL, Winter MK, McCarson KE, Wright DE, Smith PG. Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation. *J Neurosci Off J Soc Neurosci*. 2011;31(39):13728-13738. doi:10.1523/JNEUROSCI.3637-11.2011.

50. Williams BR, Thomas AJ, Collier RC, Boffeli TJ, Anderson SA. Vitamin D Levels Do Not Predict Risk of Metatarsal Fractures. *Foot Ankle Spec*. 2018;11(1):37-43. doi:10.1177/1938640017700973.