

1 **TITLE:**

2 **VITAMIN D AND FOOT AND ANKLE TRAUMA. AN INDIVIDUAL OR SOCIETAL**

3 **PROBLEM?**

4

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31 **ABSTRACT:**

32 **Background:**

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

37 **Methods:**

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

42 **Results:**

43 308 patients were included from three different centres. 66.6% were female. The  
44 average age was 47.7 (median 50, range 10 to 85). 170 patients were treated in  
45 Northampton, 80 in Chester and 58 in Leicester. The mean hydroxyvitamin-D levels  
46 were 52.0 nmol/L (SD 28.5; range 12.2 to 168.4) and the median 42.3 nmol/L. 18.8%  
47 were grossly deficient, 23.7% deficient, 34.7% insufficient and 22.7% within normal  
48 range. 351 separate bone injuries were identified of which 104 were categorised as  
49 stress reactions, 134 as stress fractures, 105 as fractures and 8 as established non-  
50 unions. Age, gender, anatomical location and fracture type did not statistically affect  
51 vitamin D levels. Ethnicity did affect Vitamin D levels: non-Caucasians mean levels  
52 were 32.4 n/mols/L compared to Caucasian levels of 53.2 nmol/L  $p=0.0026$ ). The  
53 cohorts from Northampton and Leicester were compared to the elective foot and  
54 ankle surgical patient groups who underwent pre-operative Vitamin D screening

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

57 **Conclusion:**

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

65

66 **Level of evidence:** 2b

67

68 **Keywords:**

69 Vitamin D ; Stress fracture ; Epidemiology ; Foot ; hypovitaminosis

70

71 **INTRODUCTION:**

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

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

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

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

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

103

#### 104 **METHODS:**

##### 105 **Subjects:**

106 308 patients with imaging evidence of osseous foot and ankle trauma who attended  
107 the Orthopaedic Clinics of the three senior clinicians (WJR: Northampton; PEA:  
108 Leicester; EVW: Chester) had their vitamin D blood levels (serum 25-hydroxyvitamin  
109 D (25[OH])D) measured as a routine part of their bone health assessment. The  
110 importance of vitamin D and bone health was discussed with the patients prior to  
111 testing. The results of the vitamin D measurement were reviewed with the patients  
112 at follow-up consultations and advice given to those deemed deficient relating to the  
113 importance of vitamin D supplementation.

##### 114 **Patient Demographics:**

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

**117 Vitamin D levels:**

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

**122 Serum Analysis:**

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

**132 Variables:**

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

136 Secondly, the type of injury was recorded:

- 137 • Stress reaction: This was defined as a patient presenting with pain following  
138 trauma and MRI evidence of a stress reaction within one or more bones.  
139 Patients with associated significant soft-tissue injury and with an associated

140 bone reaction, e.g. an ankle inversion injury causing lateral ligament injury  
141 and a talus bone bruise were excluded.

142 • Stress fracture

143 • Fracture

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

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

### 153 **Statistical Analysis:**

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

159 Univariate and multivariate logistic regression analysis was used to assess each  
160 independent risk factor. Vitamin D levels were used as the dependent variable.

161 Where independent variable was continuous Pearson's correlation was utilised.

162 Where independent variables were categorical either paired t-test or one-way

163 ANOVA were used. Bonferroni comparison was used where appropriate. A



164 significance level was set at  $p \leq 0.05$ . Statistical analysis was performed using STATA  
165 version 14.2 (StataCorp, TX, USA).

166

## 167 **RESULTS:**

### 168 **Patient Demographics:**

169 308 patients were included over the analysis. 66.6% were female. The mean age  
170 was 47.7 (median 50, range 10-85). 170 patients were treated in Northampton, 80  
171 in Chester and 58 in Leicester. The demographic, ethnicity and fracture  
172 characteristics between Northampton, Chester and Leicester cohorts are shown in  
173 Tables 1, 2 and 3.

### 174 **Vitamin D serum levels:**

175 The mean serum 25-hydroxyvitamin-D levels for the overall patient group was 52.0  
176 nmol/L (SD 28.5; range 12.2 to 168.4) and the median 42.3 nmol/L. By category 18.8  
177 % were grossly deficient, 23.7 % deficient, 34.7 % insufficient and 22.7 % within  
178 normal range (Table 1).

### 179 **Fracture location and type:**

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

### 183 **Sub-group analysis:**

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

**186 Age:**

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

**190 Gender:**

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

**193 Ethnicity:**

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

**197 Geographic location:**

198 Mean vitamin D levels were 57.8 (SD 29.9) for 170 patients based in Northampton,  
199 46.0 (SD 22.8) for the 80 Chester patients, and 44.3 (SD 27.7) for 58 patients based in  
200 Leicester. Northampton had a statistically significant ( $p<0.05$ ) higher vitamin D level  
201 over Chester and Leicester.

**202 Seasonal variation:**

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

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

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

216

#### 217 **DISCUSSION:**

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

230 Although experimental evidence in animals has demonstrated the benefits of  
231 Vitamin D supplementation in fracture healing,<sup>13,16,38</sup> the evidence is not so clear in

232 humans. In a systematic review of the literature, Gorter *et al* reported that having  
233 reviewed 135 publications,<sup>18</sup> Vitamin D appeared to have a role in fracture healing  
234 but that the data was inconsistent to explain how. Additionally, the knowledge of  
235 the effects of both hypovitaminosis and supplementation was scarce and  
236 inconclusive.<sup>18</sup>

237 Low Vitamin D levels are particularly prevalent in Orthopaedic Trauma patients: a  
238 study of 899 trauma patients found the overall rate of Vitamin D  
239 deficiency/insufficiency to be 77% with 39% being deficient ( $\leq 20$ ng/ml).<sup>25</sup> A small  
240 cohort of post-menopausal women with hip fractures were reported as showing a  
241 50% incidence of levels  $< 30$  nmol/L.<sup>33</sup> Two North American papers on foot and ankle  
242 fractures and Vitamin D levels warrant further analysis.<sup>35,47</sup> Miller *et al* reported on  
243 124 stress fractures, of whom 53 had Vitamin D levels measured.<sup>35</sup> The mean level  
244 was  $78.5 \pm 36.8$  nmol/L and 53% of the patients had levels  $< 75$  nmol/L. Smith *et al*  
245 reported on 75 patients with low energy foot & ankle fractures.<sup>47</sup> They found a  
246 mean Vitamin D level of  $78.2 \pm 29.5$  nmol/L and 47% of patients had levels  $< 75$   
247 nmol/L. The authors found a relationship between low Vitamin D levels and  
248 smoking, obesity and medical co-morbidities associated with hypovitaminosis D such  
249 as, chronic renal insufficiency and gastrointestinal absorption irregularities. Neither  
250 paper analysed the relationship of anatomical location or fracture type any further.  
251 Both American papers report substantially higher average Vitamin D levels in their  
252 cohorts than in this United Kingdom (UK) based paper. This is a similar trend to our  
253 previous paper on elective foot and ankle surgery patients where only 18% of  
254 patients had levels greater than 75 nmol/L compared to Bogunovic's New York  
255 elective patients where 66% had levels greater than 75 nmol/L.<sup>3,8</sup> The higher  
256 latitudes of the locations from which the UK cohort was recruited is possibly

257 influential, with an estimated level of sunshine hours per year only 60% of New  
258 York.<sup>10</sup> Routine food fortification with Vitamin D may also explain this difference.<sup>11</sup>  
259 A statistically significant seasonal variation in injury pattern was seen by Williams *et*  
260 *al*,<sup>50</sup> who looked at Vitamin D levels in patients presenting with low energy foot and  
261 ankle sprains and metatarsal fractures. Both groups had a similar proportion  
262 affected by insufficient Vitamin D levels (66% in fracture group, 71% in sprain group,  
263  $p=0.81$ ) but there were more fractures seen in the winter and sprains in the summer  
264 ( $p=0.02$ ).<sup>50</sup> A study of 5<sup>th</sup> metatarsal fractures from Wales UK, also shows similar  
265 findings, with a low mean Vitamin D level of 43.7 nmol/l (20.2 to 124.0) in 40  
266 patients.<sup>12</sup> Although there was a trend towards higher Vitamin D levels in the  
267 summer, this did not reach significance ( $p=0.06$ ).<sup>12</sup>

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

278 This raises the question of the efficacy of supplementation, on bony union, in those  
279 with hypovitaminosis D. A single, high dose, of Vitamin D (100 000 IU) in adults with  
280 long bone fractures and Vitamin D insufficiency, was not shown to have an effect on  
281 the non-union rate, compared to a control group (4% in both groups).<sup>22</sup> Other

282 studies have looked at the effect of Vitamin D alone or in combination with calcium  
283 or bisphosphonates on bone mineral density.<sup>4,15,43</sup> However, exploration of this is  
284 beyond the scope of this paper.

285 Despite analysing the foot and ankle injuries according to anatomical location, we  
286 could not identify any specific sub-group presenting with either high or low Vitamin  
287 D levels. The pattern of Vitamin D status was similar to a contemporaneous cohort  
288 of elective foot and ankle patients in two of the units studied.<sup>3</sup> The foot and ankle is  
289 a region of the body particularly prone to stress fractures. Moreover, certain groups  
290 are more likely to develop such injuries including those in the military and track and  
291 field athletes. In the military, stress fractures were reported in between 0.2% to  
292 5.2% of male recruits and 1.6% to 30% in females.<sup>1,29,31,32,42,46</sup> In track and field  
293 athletes stress fracture rates between 10 to 30% have been reported.<sup>6,28,30,42</sup> Lappe  
294 *et al* reported a 21% drop in stress fractures in female military recruits during a  
295 period of 24 months of calcium and vitamin D supplementation.<sup>32</sup> The combination  
296 of Vitamin D and Calcium has also been shown to reduce the risk of fracture in  
297 pooled analysis of 68500 patients, but there was no effect from taking just Vitamin D  
298 alone.<sup>14</sup>

299 Lack of dietary Vitamin D intake has been identified as a risk factor for stress  
300 fractures in athletes.<sup>17</sup> Giffin *et al* identified inadequate Vitamin D intake in both  
301 male & female runners compared to runners without fractures (38.8% and 45.2%  
302 respectively).<sup>17</sup> Regimens for Vitamin D supplementation within the normal  
303 population and for those with recognised hypovitaminosis have been published at  
304 home and abroad.<sup>24,27</sup> Current guidelines in the United Kingdom were recently  
305 updated by the Scientific Advisory Committee on Nutrition (July 2016). The  
306 Committee has recommended that everyone over the age of 4 years old should have

307 an RNI (Reference Nutrient Intake) of Vitamin D of 400 iu/day throughout the year.<sup>45</sup>

308 Several sporting organisations within the United Kingdom have issued dietary

309 guidelines for Vitamin D supplementation in health and following fractures.<sup>26,37</sup> The

310 dietary and supplementation advice offered to our patients with foot and ankle

311 fractures follows the advice of the English Cricket Board working party of which one

312 of the authors (WJR) was a contributor.<sup>26</sup> Patients with levels <35nmol/L should be

313 placed upon 50,000iu/week for six weeks and for levels between 35-75nmol/L

314 require 50,000iu/week for three weeks. After this period, blood levels should be re-

315 checked to assess rising vitamin D levels and further advice accordingly. For those

316 over 75nmol/L, a supplement of 1000iu/day over the winter months is

317 recommended. Our aim was to bring levels to at least 75nmol/L for patients

318 recovering from fractures.

319 Similar to previous reports, this study confirms that our foot and ankle trauma group

320 have an overall low Vitamin D profile. Four out of five patients were demonstrated

321 to have sub-optimal levels of serum Vitamin D. However, the Vitamin D distribution

322 is like a previously studied large group of foot and ankle elective patients.<sup>2</sup> This

323 suggest that either patients presenting with foot and ankle problems, whether

324 elective or trauma, tend towards low Vitamin D levels or, more probably, the

325 populations which the senior authors serve have generally low circulating levels.

326 What remains to be answered is whether these low societal levels represent a

327 significant risk factor for sustaining foot and ankle trauma? Would public health

328 measures, such as education and guidelines, to raise vitamin levels through sunlight

329 exposure and diet reduce trauma risk? Our analysis confirmed what previous work

330 has reported,<sup>2</sup> that serum Vitamin D levels are highest during the summer months.

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

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

345

346 **Conclusions:**

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



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