Foot and Ankle Surgery 25 (2019) 310–315

Contents lists available at ScienceDirect

Foot and Ankle Surgery

journal homepage: www.elsevier.com/locate/fas

Vitamin D levels in 577 consecutive elective foot & ankle surgery patients

Randeep S. Aujla[a], Patricia E. Allen[a], William J. Ribbans[b,*]

[a] Trauma & Orthopaedic Surgery, University Hospitals of Leicester, Leicester, United Kingdom
[b] The University of Northampton, Northampton, The County Clinic Northampton, England, United Kingdom

ARTICLE INFO

Article history:
Received 11 September 2017
Received in revised form 14 November 2017
Accepted 10 December 2017

Keywords:
Vitamin D
Foot & ankle surgery
Epidemiology

ABSTRACT

Background: Vitamin D deficiency is a global concern impacting upon large communities and certain disease populations. It can adversely affect the outcome of orthopaedic operations. We aimed to perform an audit of the Vitamin D status of patients in two centres in the United Kingdom undergoing elective foot and ankle surgery.

Methods: Serum 25-hydroxyvitamin-D (vitamin D) levels were obtained prospectively in 577 consecutive elective patients undergoing elective foot and ankle surgery between October 2014 and March 2017 (29 months). Variables including age, gender, ethnicity, location, season, month and procedure type were recorded.

Results: 577 patients were included over the study period. 62.0% were female. Mean age was 53.2 (median 54.5, range 16.7–86.6). 300 patients were treated in Northampton and 277 in Leicester. The serum 25-hydroxyvitamin-D levels for the patient group were normally distributed. The mean was 52.3 nmol/L (SD 28.0; range 7.5–175) and the median 47.5 nmol/L. 21.7% were grossly deficient, 31.9% deficient, 28.9% insufficient and 17.5% within normal range. Age, gender and procedure type did not statistically affect vitamin D levels ($p = 0.5$, t-test). Ethnicity, location and Winter season did affect Vitamin D levels ($p < 0.05$). August was the most significant month with levels significantly higher than January, February, March, April, June, November and December ($p < 0.05$, one-way ANOVA).

Conclusions: Only 1 in 5.7 patients had a normal Vitamin D level and 1 in 4.6 were grossly deficient. Ethnicity and patient location significantly affected Vitamin D results. Summer months were noted to demonstrate significantly the highest levels and August the highest. We did not find that age or gender affected Vitamin D levels in our cohort.

1. Introduction

Numerous studies have recognised the high global prevalence of Vitamin D deficiency, with an estimated one billion people worldwide affected [1]. According to official government figures, 21–24% of people in the United Kingdom (UK) are vitamin D deficient, with levels below 25 nmol/L [2].

Studies across various healthy populations have found vitamin D deficiency (<30 nmol/L) ranges between 12 and 52% [3–6]. Even amongst elite athletes hypovitaminosis D is common [7–10]. British subjects of Indo-Asian origin are a particular group of concern with 78–90% reported to be deficient [11,12].

The central role of serum 25-hydroxyvitamin-D (vitamin D) in calcium homeostasis, bone formation and maintenance has long been established, as is the consequences of low levels leading to secondary hyperparathyroidism and inadequate bone mineralisation. In orthopaedic surgery, hypovitaminosis D has been linked to osteoporosis and higher rates of fractures [13,14]. The consequences of hypovitaminosis D may potentially affect osteotomy and fusion surgery outcomes, impair osseointegration and place increased stress upon implants. Additionally, vitamin D deficiencies can produce muscle atrophy, weakness, arthralgia and induce neurological changes that can affect rehabilitation post-operatively [15–19]. Vitamin D has also been found to have a role in insulin sensitivity and immune system function important in infection prevention [20–22]. It has also been shown to ameliorate the symptom of fatigue in a healthy cohort during a randomised controlled trial [23].

Investigation into the effects of vitamin D deficiency is of interest not only to the medical community but the public,

* Corresponding author at: The County Clinic, 57 Billing Road, Northampton NN1 5BD, United Kingdom.
E-mail address: billribbans@billribbans.com (W.J. Ribbans).

https://doi.org/10.1016/j.fas.2017.12.007
1268-7731/

Governmental agencies and the food industry. Direct and indirect cost of vitamin D deficiency to Europe has been estimated to be in the region of €187 billion/year [24]. 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 >100 nmol/L [25]. It has even been claimed that doubling world mean vitamin D levels could be the single most cost effective way to reduce global mortality [26].

The aim of this study was to define the extent of serum 25-hydroxyvitamin-D levels in a UK cohort undergoing elective foot and ankle surgery. Additionally, we aimed to determine whether independent factors such as age, gender, ethnicity, surgery type or timing of surgery within the year presented specific risks to patients of presenting with suboptimal vitamin D levels.

2. Methods

2.1. Subjects

577 consecutive patients scheduled for admission for foot and ankle surgery under the care of two Orthopaedic Consultant Surgeons (WJR and PEA) had their vitamin D blood levels (serum 25-hydroxyvitamin D (25[OH])D) measured as a routine part of their pre-admission assessment. The period of analysis was between October 2014 and March 2017 (29 months). Only patients over the age of 16 were included.

As part of the consenting process, the importance of vitamin D and bone health was discussed with the patients.

The results of the vitamin D measurement were discussed with the patients in the perioperative period and advice given to those deemed deficient relating to the importance of vitamin D supplementation.

2.2. Patient demographics

Routine data was recorded including age, sex, ethnicity, date of blood sampling, and the nature of the foot and ankle surgery.

2.3. Vitamin D levels

The literature varies in agreeing upon a classification for normality and deficiency of serum vitamin D levels. In keeping with previous authors we defined normal as >75 nmol/L; insufficiency as 50–75 nmol/L; deficiency as less than 31–50 nmol/L; and grossly deficient as less than 30 nmol/L [27–29].

2.4. Serum analysis

Samples were analysed at the Pathology Departments of Northampton General Hospital (NGH) and Leicester General Hospital (LGH). An assay of the serum 25-hydroxyvitamin-D levels was taken and the results feed 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. Its lower limit of detection was 7.5 nmol/L although several received results simply stated <10.5 nmol/L. In these cases 10.5 nmol/L was taken as the result.

The Leicester biochemistry laboratory uses the ADVIA Centaur XPT machine to perform immunoassays for serum 25-hydroxyvitamin-D levels. The lower limit of detection here was 15 nmol/L and thus in patients with a result of <15 nmol/L, 15 nmol/L was taken as the result.

2.5. Variables

Age was identified at time of blood test. Sub-groups of age used for analysis were <30, 30–49, 50–69 and >70. Ethnicity was defined as Caucasian and non-Caucasian. The non-Caucasian group included South Asian, Far Eastern and Afro-Caribbean patients. Seasons were defined as Winter (January, February, March), Spring (April, May, June), Summer (July, August, September) and Autumn (October, November, December). Procedure type were categorised as fusion, osteotomy, other bone/joint surgery or soft tissue surgery. Where there were multiple procedures, the procedure most likely to be affected by hypovitaminosis (as listed in the previous sentence) was used to identify the procedure type. The senior author (WJR) decided the most significant procedure type where multiple procedures were performed.

2.6. Statistical analysis

The serum 25-hydroxyvitamin D assay results for the 577 patients were subjected to statistical analysis. The results were analysed separately for each Orthopaedic Unit and together. The mean, median and standard deviation was determined and proportion of patients categorised as normal, insufficient, or deficient were 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

Table 1
A table to show the difference in demographics, ethnicity and procedure type between the Northampton and Leicester cohorts.

		Northampton		Leicester		Total	
		Number	%	Number	%	Number	%
Demographics	Male	128	42.7	91	32.9	219	38.0
	Female	172	57.3	186	67.1	358	62.0
	Mean age	49.3 (16.7–86.4)		57.5 (18.1–86.6)		53.2 (16.7–86.6)	
Ethnicity	Caucasian	291	97.0	250	90.3	541	93.8
	South Asian	3	1.0	25	9.0	28	4.9
	Afro-Caribbean	6	2.0	1	0.4	7	1.2
	Far Eastern	0	0	1	0.4	1	0.2
Procedure type	Fusion	71	23.7	131	47.3	202	35.0
	Osteotomy	52	17.3	43	15.5	95	16.5
	Soft tissue	44	14.7	45	16.2	89	15.4
	Other bone/joint	133	44.3	58	20.9	191	33.1

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

3. Results

3.1. Patient demographics

577 patients were included over the study period. 62.0% were female. Mean age was 53.2 (median 54.5, range 16.7–86.6). 300 patients were treated in Northampton and 277 in Leicester. The demographic, ethnicity and procedure type differences between Northampton and Leicester cohorts are shown in Table 1.

3.2. Vitamin D serum levels

The serum 25-hydroxyvitamin-D levels for the patient group were normally distributed. The mean was 52.3 nmol/L (SD 28.0; range 7.5–175) and the median 47.5 nmol/L. 21.7% were grossly deficient, 31.9% deficient, 28.9% insufficient and 17.5% within normal range (Fig. 1).

3.3. Risk factors for hypovitaminosis D

Table 2 demonstrates the mean vitamin D levels for various sub-groups.

3.3.1. Age

Table 2 highlights the differences between age brackets <30, 30–49, 50–69 and >70 (one-way ANOVA). No statistical difference was found between age groups. There was no correlation with age and vitamin D level (−0.0021, Pearson's correlation). When comparing patients <50 and >50 years of age there was no statistical difference in mean vitamin D levels ($p = 0.64$, unpaired *t*-test).

3.3.2. Gender

Gender did not statistically affect vitamin D levels ($p = 0.5$, *t*-test). This was the case for both locations and the patients overall.

3.3.3. Ethnicity

Mean vitamin D levels were 53.1 (SD 28.4) for 541 Caucasians and 41.1 (SD 19.1) for 36 non-Caucasian patients ($p < 0.05$, *t*-test).

Table 2
A table to show the vitamin D levels for various sub-groups in multiple variables.

Variable	Subgroup	Number	Mean vit D level	SD	*p* value
Age	<30	60	54.9	26.8	
	30–49	146	50.3	28.1	
	50–69	293	53.4	28.8	
	>70	78	49.9	25.8	NS
Gender	Male	219	52.1	27.7	
	Female	358	52.4	28.2	NS
Ethnicity	Caucasian	541	53.1	28.4	
	Non-Caucasian	36	41.1	19.1	$p < 0.05$
Location	Leicester	277	45.3	20.9	
	Northampton	300	58.8	31.9	$p < 0.05$
Season	Winter	191	46.4	24.9	
	Spring	117	49.2	29.3	
	Summer	126	64.4	33.0	$p < 0.05$
	Autumn	143	52.0	22.7	
Procedure type	Fusion	202	51.1	26.6	
	Osteotomy	95	52.1	29.7	
	Soft Tissue	89	53.8	28.5	
	Other	191	52.2	28.6	NS

3.3.4. Location

Mean vitamin D levels were 58.8 (SD 31.9) for 300 patients based in Northampton and 45.3 (SD 20.9) for 277 patients based in Leicester ($p < 0.05$, *t*-test).

3.3.5. Month

Fig. 2 shows the distribution of vitamin D levels across the months of the year. August was most significant month with levels significantly higher than January, February, March, April, June, November and December ($p < 0.05$, one-way ANOVA).

3.3.6. Season

Vitamin D levels divided by season did vary with the Summer months having significantly higher levels than other seasons ($p < 0.05$, one-way ANOVA).

3.3.7. Procedure type

Type of procedure did not correlate with vitamin D levels ($p > 0.05$, one-way ANOVA).

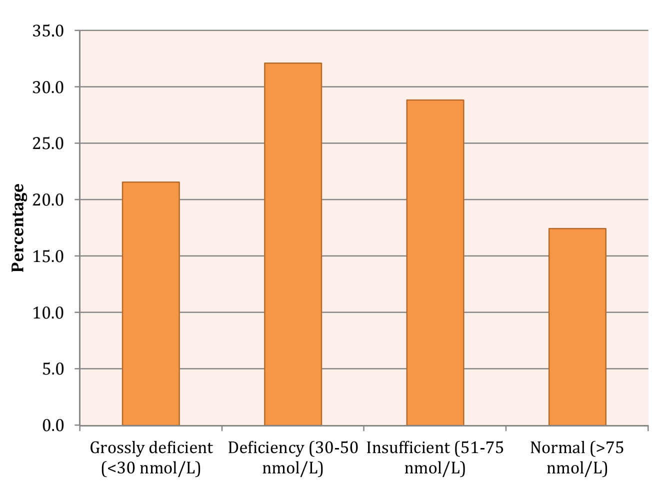

Fig. 1. A figure to demonstrate the frequencies of vitamin D levels according to category.

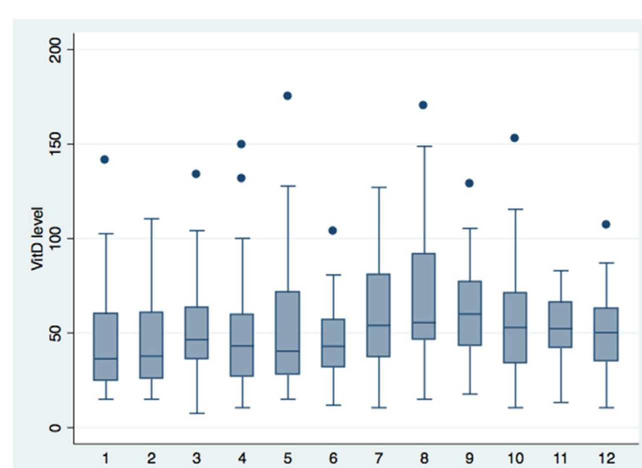

Fig. 2. A box plot to show the spread of vitamin D levels across months.

3.3.8. Multivariate analysis

A multiple regression was run to predict vitamin D levels from age, gender, ethnicity, location, surgery type, month and season. These variables statistically significantly predicted vitamin D levels, $F(12, 564) = 6.84$, $p < 0.005$, $R^2 = 0.127$. Ethnicity, location, Summer season and the month of August added statistical significance to the prediction, $p < 0.05$.

4. Discussion

Although there are numerous epidemiological publications on the global prevalence of vitamin D insufficiency and deficiency, there is relatively little published work on the status of patients presenting for orthopaedic surgery in general, and foot and ankle procedures specifically.

We present the results of a prospective study of a United Kingdom cohort undergoing elective foot and ankle surgery. We have demonstrated that only 18% of patients had a normal range vitamin D level and 22% were grossly deficient. Age, gender or surgery type did not affect vitamin D levels. Non-Caucasian ethnicity and winter months had significantly lower vitamin D levels.

We demonstrated a mean vitamin D level of 52.3 nmol/L (SD 28.0, 95% CI 50.0–54.6). 18% had vitamin D levels above normal (>75 nmol/L). In contrast Bogunovic et al found normal levels in 66% of their 192 foot and ankle patients in New York, USA [28]. Our cohort had notably lower number of patients within the normal range. There could be a multitude of reasons for this but it is likely that geographical location, and its sunshine exposure, is the underlying cause for this difference. The East Midlands has a latitude of 53° and averages between 1400 and 1600 h of sunshine per year [30]. New York's latitude is 41° and about 2500 h of sunshine per year.

Maier et al published the largest study pertaining to vitamin D in orthopaedic patients [27]. They reviewed 1119 orthopaedic patients from Germany. 84% of patients had levels <75 nmol/L and 60% with levels <50 nmol/L. This was similar to our finding of 82.6% of patients having vitamin D levels <75 nmol/L. This German cohort closely matches our cohort in terms of geographical exposure to sunshine.

In a comparable UK study, Smith et al found Vitamin D levels <30 nmol/L in 47% of foot and ankle fracture patients compared to our finding of 22% in elective patients [31]. It is understandable that patients presenting for fractures (including stress fractures) would have a lower level of bone health. Ball et al. (2014) reported a small series of foot and ankle non-unions of fusions whose Vitamin D status was compared to patients with successful fusions. The non-union group had statistically significantly lower levels (mean of 58 nmol/L) compared to the successful group (mean of 90 nmol/L). If this finding were to be replicated in a larger series it would suggest that levels of circulating Vitamin D reported by UK laboratories as being within normal limits (<50 nmol/L) still place patients at risk of non-union. Similarly, it suggests that all fusion non-unions should be investigated for Vitamin D status and makes a strong case for pre-operative screening in this group [32].

Glowacki reported that 10.3% of 68 females undergoing total hip replacement for osteoarthritis had serum 25-hydroxyvitamin-D levels <30 nmol/L [33]. The same group found that 50% of 30 females presenting with hip fractures had serum 25-hydroxyvitamin-D levels <30 nmol/L [34]. Again reinforcing the principle that trauma patients will have lower vitamin D levels compared to elective counterparts.

Spinal fusion rates have been shown to be affected by hypovitaminosis D [35,36].

Rodriguez et al advised that it was imperative that all patients undergoing spinal fusions should have serum Vitamin D levels maintained at more than 75 nmol/L [37]. Brinker reported that 68% of 37 patients investigated for unexplained fracture non-unions were Vitamin D deficient [38]. Patton et al recommended screening for all orthopaedic patients undergoing arthroplasty, spine or trauma surgery, non-union patients, and patients with osteoporosis and other acknowledged risk factors [39].

We did not find that age or gender affected vitamin D levels in our cohort. Other studies have supported this view, and a meta-regression analysis finding that age and gender did not affect vitamin D levels across 394 studies [27,40]. Nevertheless there are conflicting results to be found in the literature. Bogunovic et al. found that patients younger than 50 and males had lower levels of vitamin D in their American cohort [28]. Other studies have concluded that males have lower levels also [41]. A global summary paper found that females and older age were associated with lower levels of serum 25-hydroxyvitamin-D levels [42].

The effect of darker skin/ethnicity has been widely understood across multiple studies in literature [42]. Our findings concur with this with only 5.6% of non-Caucasian patients having vitamin D levels >75 nmol/L. Non-Caucasians had a mean vitamin D level 12 nmol/L lower than Caucasians with a narrow standard deviation. Gordon et al, assessing an American cohort, found that African-Americans had an increased odds ratio of 8.59 for being vitamin D deficient and that ethnicity was an independent predictor of hypovitaminosis D [4]. Other studies have supported this well understood phenomenon [43–45].

Our patient cohort was derived from two municipalities in central England. Although both centres lie within the East Midlands and are only 38 miles apart, the communities have different ethnic demographics. In Leicester, 51% of the population is White; 37% Asian; 6% Black; and 6% from other groups. For Northampton, the respective proportions are 85%; 6%; 5%; and 4% (2011 UK National Population census). This was reflected in the ethnic diversity of the two surgical groups audited. However, location was an independent risk factor for predicting vitamin D levels. The explanation for this is multi-factorial. Both centres used different laboratories, machines and techniques for assessing serum samples and this may have led to some variation in calibration and interpretation. All patients from the Leicester group were National Health Service patients and all from Northampton were private patients. A difference that could be implied from these differences are that private patients tend to be more affluent. This may be associated with higher quality of life, improved education and a culture to prioritise good health practices.

The “Vitamin D winter” as defined by the period of time when the UV index does not rise above 3 lasts from the end of September to the end of March (six months) according to weather forecasting data (*WeatherPro*). For this reason we took winter as between January and March in our seasonal analysis. We demonstrated that Summer months (July, August, September) had a significantly higher vitamin D level that other seasons. This is likely to influence our interpretation of results depending on when in the year they were taken. This provides us with further information to critically analyse a patient's bone health.

The widespread reporting of hypovitaminosis D in large areas of the world represents an issue of major global public health concern. There is no consensus on what levels of circulating serum 25-hydroxyvitamin-D levels constitutes deficiency, insufficiency or normal. Many laboratories in the UK use 50–150 nmol/L (20–60 ng/ml) as the normal range with insufficiency in the 30–50 nmol/L, and deficiency at less than 30 nmol/L. Conversely, expert guidelines frequently recommend levels greater than 75 nmol/L for optimal serum 25-hydroxyvitamin-D level with less than 50 nmol/L representing a deficiency [1,29,46]. Normal levels above 75–80 nmol/L have been used in other orthopaedic surgery publications [27,28].

We accept some limitations within our study. Firstly, the specimens were analysed in two separate local biochemistry departments, which will lead to some variation in results. It is acknowledged that variations can be found between laboratories. When the result was reported as (<10.5 nmol/L) we recorded this result as 10.5 nmol/L exactly in order to perform statistical analysis. This would falsely raise the mean vitamin D levels as the actual result. However, the difference is likely to be small and have minimal effect upon overall means. The audit did not set out to analyse the effects of hypovitaminosis D on complication rates and ultimate outcomes of the surgery as deficient patients were advised of the findings and remedial advice given in the perioperative period. The study attempted to identify the scale of the problem in this cohort and seek indicators of potential high-risk groups and to guide advice in general to our surgical patients. Another issue raised was that we did not analyse the patients taking vitamin D supplementation pre-operatively. The number was believed to be small and the dosage taken and compliance variable Meaningful analysis was deemed impossible.

Low vitamin D levels are evident in orthopaedic surgery, as we have shown, but the exact impact on patient outcomes remains unclear. It may adversely affect a patient's pain, related to both bone and soft tissue, leading to lower thresholds for surgical intervention. It may also impact on the outcomes of certain operations such as fusions and osteotomies. There needs to be a consensus regarding exact definition of what constitutes deficiency, insufficiency and normal levels along with a uniform reporting unit. This will aid communication across medical specialities when discussing this evolving entity.

5. Conclusions

In our cohort of pre-operative foot and ankle elective patients, only 1 in 5.7 patients had a normal Vitamin D level and 1 in 4.6 were grossly deficient. Ethnicity and patient location significantly affected Vitamin D results. Summer months were noted to demonstrate significantly the highest levels and August the highest of all. We did not find that age or gender affected Vitamin D levels in our cohort. We feel our findings can assist in the assessment of elective foot and ankle patients and would recommend screening of at risk patients to optimise their bone health pre-operatively.

Conflict of interest

All named authors hereby declare that they have no conflicts of interest to disclose.

Acknowledgments

We thank Jonathan White (T&O Registrar) for undertaking initial data analysis of the pilot study.

References

[1] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266–81.
[2] Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, 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.
[3] Chapuy M-C, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997;7(5):439–43.
[4] Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004;158(6):531–7.
[5] Hill TR, Cotter AA, Mitchell S, Boreham CA, Dubitzky W, Murray L, et al. Vitamin D status and its determinants in adolescents from the Northern Ireland Young Hearts 2000 cohort. Br J Nutr 2008;99(05):1061–7.
[6] Macdonald HM, Mavroeidi A, Barr RJ, Black AJ, Fraser WD, Reid DM. Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D. Bone 2008;42(5):996–1003.
[7] Pollock N, Dijkstra P, Chakraverty R, Hamilton B. Low 25 (OH) vitamin D concentrations in international UK track and field athletes. South Afr J Sports Med [Internet] 201224(2) Available from: http://www.ajol.info/index.php/sasma/article/download/78022/68416 [cited 3.11.16].
[8] Farrokhyar F, Tabasinejad R, Dao D, Peterson D, Ayeni OR, Hadioonzadeh R, et al. Prevalence of vitamin D inadequacy in athletes: a systematic-review and meta-analysis. Sports Med 2015;45(3):365–78.
[9] Close GL, Russell J, Cobley JN, Owens DJ, Wilson G, Gregson W, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci 2013;31(4):344–53.
[10] Constantini NW, Arieli R, Chodick G, Dubnov-Raz G. High prevalence of vitamin D insufficiency in athletes and dancers. Clin J Sport Med 2010;20(5):368–71.
[11] Serhan E, Newton P, Ali HA, Walford S, Singh BM. Prevalence of hypovitaminosis D in Indo-Asian patients attending a rheumatology clinic. Bone 1999;25(5):609–11.
[12] Pal BR, Marshall T, James C, Shaw NJ. Distribution analysis of vitamin D highlights differences in population subgroups: preliminary observations from a pilot study in UK adults. J Endocrinol 2003;179(1):119–29.
[13] Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med 2006;260(3):245–54.
[14] Fisher A, Srikusalanukul W, Davis M, Smith P. Hip fracture type: important role of parathyroid hormone (PTH) response to hypovitaminosis D. Bone 2010;47(2):400–7.
[15] Prineas JW, Mason AS, Henson RA. Myopathy in metabolic bone disease. Br Med J 1965;1(5441):1034.
[16] Al-Said YA, Al-Rached HS, Al-Qahtani HA, Jan MM. Severe proximal myopathy with remarkable recovery after vitamin D treatment. Can J Neurol Sci Can Sci Neurol 2009;36(03):336–9.
[17] Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo clinic proceedings [Internet]. Elsevier; 2003. p. 1463–70 Available from: http://www.sciencedirect.com/science/article/pii/S0025619611627420 [cited 3.11.16].
[18] Tague SE, Clarke GL, Winter MK, McCarson KE, Wright DE, Smith PG. Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation. J Neurosci 2011;31(39):13728–38.
[19] Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 2016;176(2):175–83.
[20] Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. J Mol Med 2010;88(5):441–50.
[21] Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311(5768):1770–3.
[22] Girgis CM, Clifton-Bligh RJ, Turner N, Lau SL, Gunton JE. Effects of vitamin D in skeletal muscle: falls, strength, athletic performance and insulin sensitivity. Clin Endocrinol (Oxf) 2014;80(2):169–81.
[23] Nowak A, Boesch L, Andres E, Battegay E, Hornemann T, Schmid C, et al. Effect of vitamin D3 on self-perceived fatigue: a double-blind randomized placebo-controlled trial. Medicine (Baltimore) 201695(52).
[24] Grant WB, Cross HS, Garland CF, Gorham ED, Moan J, Peterlik M, 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):104–13.
[25] 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. Dermatoendocrinology 2016;8(1):e1248324.
[26] Grant WB. An estimate of the global reduction in mortality rates through doubling vitamin D levels. Eur J Clin Nutr 2011;65(9):1016–26.
[27] Maier GS, Jakobs P, Roth KE, Kurth AA, Maus U. Is there an epidemic vitamin D deficiency in German orthopaedic patients? Clin Orthop Relat Res 2013;471(9):3029–35.
[28] Bogunovic L, Kim AD, Beamer BS, Nguyen J, Lane JM. Hypovitaminosis D in patients scheduled to undergo orthopaedic surgery. J Bone Jt Surg Am 2010;92(13):2300–4.
[29] Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev 2005;10(2):94–111.
[30] Midlands: climate [Internet]. Met Office. 2017 Available from: http://www.metoffice.gov.uk/climate/uk/regional-climates/mi [cited 14.06.17].
[31] 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.

[32] Ball TA, Readman HF, Kendal A, Rogers MJ, Sharp R, Lavis G, et al. Vitamin D deficiency and nonunion in foot and ankle surgery. Bone Jt J 2014;96(Suppl. 17):32.
[33] Glowacki J, Hurwitz S, Thornhill TS, Kelly M, LeBoff MS. Osteoporosis and vitamin-D deficiency among postmenopausal women with osteoarthritis undergoing total hip arthroplasty. J Bone Jt Surg Am 2003;85(12):2371–7.
[34] 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):1505–11.
[35] Metzger MF, Kanim LE, Zhao L, Robinson ST, Delamarter RB. The relationship between serum vitamin D levels and spinal fusion success: a quantitative analysis. Spine 2015;40(8):E458.
[36] Stoker GE, Buchowski JM, Bridwell KH, Lenke LG, Riew KD, Zebala LP. Preoperative vitamin D status of adults undergoing surgical spinal fusion. Spine 2013;38(6):507–15.
[37] Rodriguez WJ, Gromelski J. Vitamin D status and spine surgery outcomes. ISRN Orthop [Internet] 2013 Available from: http://downloads.hindawi.com/journals/isrn.orthopedics/2013/471695.pdf [cited 3.11.16].
[38] Brinker MR, O'Connor DP, Monla YT, Earthman TP. Metabolic and endocrine abnormalities in patients with nonunions. J Orthop Trauma 2007;21(8):557–70.
[39] Patton CM, Powell AP, Patel AA. Vitamin D in orthopaedics. J Am Acad Orthop Surg 2012;20(3):123–9.
[40] Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, et al. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 2009;20(1):133.
[41] Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of vitamin D status on body mass index, gender, age and season. Anticancer Res 2009;29(9):3713–20.
[42] Mithal A, Wahl DA, Bonjour J-P, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 2009;20(11):1807–20.
[43] Perry HM, Miller DK, Morley JE, Horowitz M, Kaiser FE, Perry HM, et al. A preliminary report of vitamin D and calcium metabolism in older African Americans. J Am Geriatr Soc 1993;41(6):612–6.
[44] Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 is related to physical activity and ethnicity but not obesity in a multicultural workforce. Intern Med J 1995;25(3):218–23.
[45] Harris SS, Soteriades E, Coolidge JAS, Mudgal S, Dawson-Hughes B. Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population 1. J Clin Endocrinol Metab 2000;85:4125–30.
[46] Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005;135(2):317–22.