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ORIGINAL STUDY

Vitamin D, calcium and albumin bloodserum levels in Belgian orthopedic patients – is systematic screening justified?

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In the setting of fracture care, orthopedic surgeons are primarily focused on treating the fracture itself, but more and more attention is being paid to prevention of such fractures and identifying risk factors associated with worse postoperative prognoses. In our study we collected postoperative vitamin D, calcium and albumin bloodserum levels from 163 patients who were admitted with a femur fracture and from 233 patients who were admitted for an elective hip arthroplasty during the period of 365 days.

***Results*: 84.21% of the fracture population had a vitamin D deficiency (< 20 ng/mL) as well as 77.30% of the elective hip arthroplasty population. There were no significant seasonal differences in the fracture population. 80.27% of the fracture population had an albumin deficiency (< 29 g/L) compared to 38.75% of the reference population. There were no significant statistical differences in vitamin D and albumin bloodserum levels between the under 75 years old age group and the over 75 years old age group. We can make the tentative assumption that systematic screening for all hip fracture patients and all elective hip arthroplasty patients admitted to our orthopedic ward – independent of their age, season or pathology – is justified and we advise other hospitals to implement this as well.**

Keywords : Vitamin D ; calcium ; albumin ; femur fracture ; hip fracture ; total hip arthroplasty ; hip resurfacing arthroplasty.

INTRODUCTION

Fracture care is one of the main focusses in orthopedic surgery. However, many authors believe that fracture prevention and osteoporosis treatment are equally important. The socio-economic burden of fractures has been studied extensively and should not be underestimated *(8,13)*. Furthermore, they also lead to significant morbidity with important temporary or permanent disability, physically as well as psychosocially *(8,13)*. Fifty percent of patients suffering from hip fractures lose the ability to walk without assistance and 25% will require domiciliary care postoperatively. Mortality rate within six months after hip fractures has been reported to be as high as 30% *(8,13)*.

Many factors have been identified as predisposing risk factors for hip and femur fractures. Three important factors that can be investigated through

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blood tests are vitamin D, calcium and albumin serum levels. A vitamin D deficiency is correlated with osteoporosis and osteoporotic hip and femur fractures because a deficiency not only increases the amount of non-mineralized bone matrix but can also cause negative changes in the mineralized bone tissue *(11,13,15,18)*. Vitamin D and calcium supplement therapy are often prescribed for patients with known osteoporosis, although the diagnosis is frequently only clear after occurrence of a fracture and supplement therapy is therefore started too late *(13)*.

Albumin is widely recognized as a good predictive biochemical value for poor nutritional status *(3)*. A 2014 retrospective observational study by Harrison et al. researched whether or not early identification of patients with hypoalbuminemia on admission could optimize the mortality rates in patients with a femur neck fracture *(8)*. Hypoalbuminemia is a statistically significant risk factor for mortality and surgical site infection after hip fracture *(7,19)* and Harrison et al. showed that survival was the greatest in the group of patients with normal albumin levels *(8,17)*. Possible complications due to hypoalbuminemia include decubitus ulcers, poor wound healing and infection secondary to leg edema. Silva et al. report a mortality rate of 28.9% in these patients *(4,17)*. Specifically regarding hip fractures, Pimlott et al. showed that short-term mortality was 2.5 times more likely in patients with hypoalbuminemia and the chance of developing a post-operative complication was twice as high *(16)*.

A 2016 cross-sectional observational study showed significantly higher odds of osteoporosis at the femoral neck and total femur in patients with hypoalbuminemia (<35 g/L) compared to those with an albumin level of >40g/L. It was concluded that hypoalbuminemia is independently associated with osteoporosis at the femoral neck and total femur in the general American population *(1)*.

Our objective was to observe vitamin D, calcium and albumin bloodserum levels in a specific hip and femur population in our hospital according to different months of the year and different age groups, and to determine whether systematic screening should be carried out in our hospital.

MATERIALS AND METHODS

The aim of the study was to observe vitamin D, calcium and albumin bloodserum levels in patients presenting with a proximal femur, periprosthetic femur, or femur shaft fracture. We wanted to compare these results with those of a control group consisting of all patients undergoing elective hip arthroplasty in our unit. We aimed to determine whether the fracture population (FP) had more vitamin D deficiencies than the reference population (RP). We also aimed to determine whether there were more vitamin D deficiencies in the months of the year with the least sunlight exposure compared to the months with the highest sunlight exposure. Vitamin D, calcium and albumin bloodserum levels were compared according to different age groups.

We performed a prospective observational study in a level 2 hospital in Belgium. The study period was determined between January 22nd 2017 and January 21st 2018. A first database was collected consisting of all patients presenting with a proximal femur, periprosthetic femur or femur shaft fracture. A second data set was collected in which all patients undergoing elective hip arthroplasty (both total and resurfacing) during the study period were included. The study was submitted to the ethical committee of our hospital.

In the fracture group, all patients were admitted to our ward through the emergency department. We collected blood samples including serum vitamin D (25(OH)D), calcium and albumin levels of all patients on postoperative day 1. We also noted if patients were already on vitamin D supplement and/or osteoporosis treatment (either D-cure and/or Steovit D3) prior to admission.

In the control group, we included all patients undergoing elective hip replacement surgery, either a total hip arthroplasty (THA) or resurfacing. All elective surgery was performed by one of our two hip surgeons (JDS or JVDS). Blood samples were collected from these patients on postoperative day 2, including serum vitamin D (25(OH)D), calcium and albumin levels. We also noted if patients were already on vitamin D supplement and/or osteoporosis treatment (either D-cure, Steovit D3, Calx plus or Alpha 1 Leo) prior to admission.

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Table I. — Overall results vitamin D and calcium levels in the fracture population without vitamin D supplement therapy upon admission and the fracture population under vitamin D supplement therapy

Fracture population	**Without vitamin D supplement therapy**		**With vitamin D supplement therapy**	
	Vitamin D	**Calcium**	**Vitamin D**	**Calcium**
n =	133	128	29	27
Median (ng/mL)	8.7	2.14	27.7	2.15
IQR (ng/mL)	6.7-14.3	2.06-2.24	24.7-33.3	2.08-2.21
no. of patients with a deficiency	112	53	5	9
% of patients with a deficiency	84.21%	41.41%	17.24%	33.33%

Table II. — Overall results vitamin D and calcium levels in the reference population without vitamin D supplement therapy upon admission and with vitamin D supplement therapy

Reference population	**Without vitamin D supplement therapy**		**With vitamin D Supplement therapy**	
	Vitamin D	**Calcium**	**Vitamin D**	**Calcium**
n =	163	163	16	17
Median (ng/mL)	11.1	2.17	16.65	2.23
IQR (ng/mL)	7.8-18.7	2.12-2.24	10.33-20.03	2.1-2.31
no. of patients with a deficiency	126	39	12	5
% of patients with a deficiency	77.30%	23.93%	75.00%	29.41%

A first analysis was performed on the presence of vitamin D, calcium and albumin deficiencies in both groups. We also analysed the influence of age on the presence of deficiencies, by dividing both groups in to two different age groups – under 75 years old and 75 years or older.

A second analysis was performed to determine the influence of sunlight and investigate seasonal variations in vitamin D, calcium and albumin deficiencies. The period with most hours of daylight was defined as May, June and July. The period with the least hours of sunlight was defined as November, December and January. We compared presence of vitamin D, calcium and albumin deficiencies during these two periods of time.

In our laboratory, cut off values implying a deficiency are < 20 ng/mL for vitamin D, < 2.12 mmol/L for calcium and < 29 g/L for albumin.

The D'Agostino and Pearson normality test was used for continuous data. Continuous normally distributed data are presented as a mean with standard deviation, non-normally distributed data as a median with interquartile range. Group means were compared using unpaired, two-tailed t-test for normally distributed variables and Mann-Whitney U test for non normally distributed variables. One-way ANOVA and Kruskall-Wallis one way analysis were used to compare multiple groups in case of normally and non-normally distributed variables, respectively. GraphPad Prism 6.0 software (San Diego, CA, USA) was used for statistical analysis and a p-value < 0.05 was considered statistically significant.

RESULTS

133 patients were included in the fracture patient population who were not under vitamin D supplement therapy upon admission. The average age was 78.9 years old (range 39-97 years). 84.21% had a vitamin D deficiency, and 41.41% had a calcium deficiency. 29 patients were included in the fracture patient population who were already under vitamin D supplement therapy upon admission. The average age was 83.3 years old (range 64-94 years). 17.24% had a vitamin D deficiency, and 33.33% had a calcium deficiency (table I).

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Table III. — Albumin bloodserum levels
in the fracture and reference population

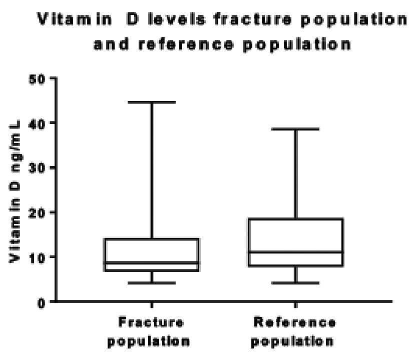

Figure 1. — Vitamin D levels fracture and reference population not under supplement therapy.

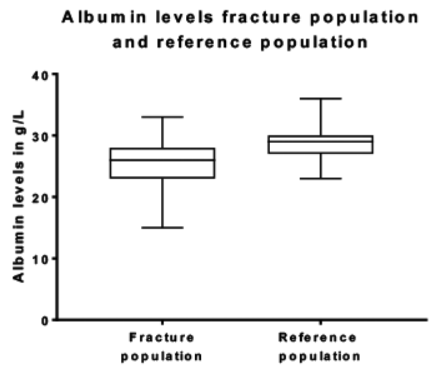

Figure 2. — Albumin bloodserum levels in the fracture population and reference population.

Table III. — Albumin bloodserum levels in the fracture and reference population

Albumin levels	Fracture population	Reference population
n =	147	160
Median (ng/mL)	26.00	29
IQR (ng/mL)	23-28	27-30
no. of patients with a deficiency	118	62
% of patients with a deficiency	80.27%	38.75%

Non-parametric tests showed that there was a statistical significant difference in vitamin D values between the two fracture populations ($p < 0.0001$) i.e. with and without vitamin D supplement therapy. There was no significant difference between the two fracture populations for calcium levels ($p = 0.7576$).

163 patients were included in the reference population who were not under any form of vitamin D supplement therapy upon admission. The average age was 66.9 years old (range 27-92 years). 77.30% had a vitamin D deficiency and 23.93% a calcium deficiency. 16 patients were included in the reference population already under vitamin D supplement therapy upon admission. The average age was 76.4 years old (range 58-89 years). 75.00% had a vitamin D deficiency and 29.41% had a calcium deficiency (table II).

Non-parametric testing showed that there was a statistical significant difference in vitamin D levels between the two reference populations ($p = 0.0438$) i.e. with and without vitamin D supplement therapy. Non-parametric testing showed that there was a statistical significant difference ($p = 0.0042$) in vitamin D levels between the fracture population not under vitamin D supplement therapy and the reference population not under vitamin D supplement therapy (figure 1).

147 patients were included in the fracture population for albumin bloodserum level analysis. 80.27% of the patients had a value < 29 g/L. 160 patients were included in the reference population when albumin levels were evaluated. 38.75% of the patients had a deficiency (table III).

Non-parametric tests showed that there was a significant difference in albumin levels in the fracture population compared to the reference population ($p < 0.0001$) (figure 2).

31 patients were included in the fracture population not under supplement therapy when we looked at vitamin D levels in the months with the most hours of sunlight (May-June-July). 90.32% had deficiency and the median value was 8.5 ng/mL. 35 patients were included in the months with the least hours of sunlight (November-December-January). 88.57% had a deficiency (table IV). There was no statistical significant seasonal difference ($p = 0.3933$) in the fracture population. 54 patients were included in the reference population not under supplement therapy when we looked at vitamin D levels in the months with the most hours of sunlight. 70.37% had deficiency and the median value was 12.6 ng/mL. 41 patients were included in the

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Table IV. — Vitamin D bloodserum levels in the fracture population not under vitamin D supplement therapy in the months with the most hours of sunlight and the months with the least hours of sunlight and vitamin D bloodserum levels in the reference population not under vitamin D supplement therapy.

	Fracture population		Reference population	
	Most hours of sunlight (May-Jun-Jul)	Least hours of sunlight (Nov-Dec-Jan)	Most hours of sunlight (May-Jun-Jul)	Least hours of sunlight (Nov-Dec-Jan)
n =	31	35	54	41
Median (ng/mL)	8.5	8.9	12.6	10.2
IQR (ng/mL)	6.8-13	6.9-15.2	8.1-21.98	6.35-14.45
no. of patients with a deficiency	28	31	38	37
% of patients with a deficiency	90.32%	88.57%	70.37%	90.24%

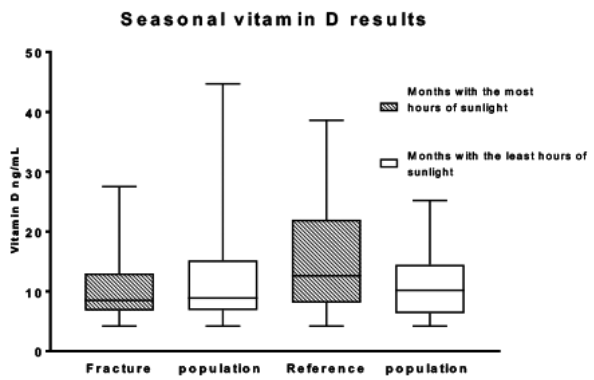

Figure 3. — Vitamin D levels for the fracture and reference population according to age.

months with the least hours of sunlight. 90.24% had a deficiency (table IV). There was a statistical significant seasonal difference (p = 0.0202) in the reference population.

Non-parametric testing showed there was a statistical significant difference (p = 0.0038) in vitamin D levels in the months with the most hours of sunlight exposure in the fracture population compared to the reference population. There was no statistical significant difference (p = 0.8541) between the two populations in the months with the least hours of sunlight exposure (figure 3).

In the fracture population of patients not under vitamin D supplement therapy 42 patients were included in the younger than 75 years old age group. 80.95% of the patients had a Vitamin D deficiency compared to 85.71% of the patients 75 years and older (table V). There was no statistical significant difference (p = 0.0899) in vitamin D level between the two age groups.

In the reference population of patients not under vitamin D supplement therapy 115 patients were included in the younger than 75 years old age group. 77.39% of the patients had a deficiency which was similar to 77.08% of the patients 75 years and older (table VI). There was no statistical significant difference (p = 0.1205) in vitamin D level between the two age groups.

Table V. — Vitamin D and calcium levels in the fracture population not under vitamin D supplement therapy according to age

	< 75 years old		≥ 75 years old	
	Vitamin D	Calcium	Vitamin D	Calcium
n =	42	41	91	87
Median (ng/mL)	9.25	2.18	8.5	2.13
IQR (ng/mL)	7.275-15.83	2.09-2.25	6.1-13	2.04-2.2
no. of patients with a deficiency	34	14	78	39
% of patients with a deficiency	80.95%	34.15%	85.71%	44.83%

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Table VI. — Vitamin D and calcium levels in the reference population not under vitamin D supplement therapy according to age

	< 75 years old		≥ 75 years old	
	Vitamin D	**Calcium**	**Vitamin D**	**Calcium**
n =	115	114	48	49
Median (ng/mL)	12.1	2.17	9.1	2.16
IQR (ng/mL)	8.1-18.8	2.12-2.25	7.55-17.68	2.11-2.23
no. of patients with a deficiency	89	26	37	13
% of patients with a deficiency	77.39%	22.81%	77.08%	26.53%

Table VII. — Albumin bloodserum levels in the fracture population according to age and albumin bloodserum levels in the reference population according to age

	Fracture population		Reference population	
	< 75 years	**≥ 75 years**	**< 75 years**	**≥ 75 years**
n =	44	103	109	51
Median (ng/mL)	26	26	29	29
IQR (ng/mL)	22.25-28	23-28	28-31	27-30
no. of patients with a deficiency	35	83	39	23
% of patients with a deficiency	79.55%	80.59%	35.78%	45.10%

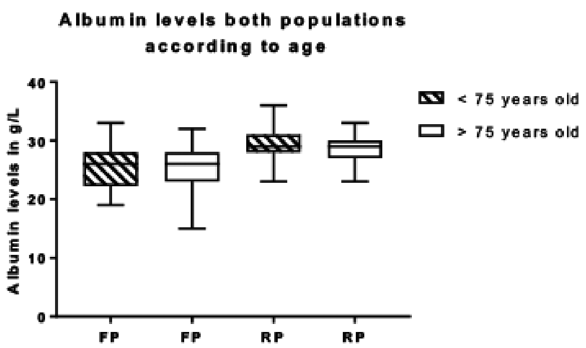

Figure 4. — Albumin levels for both populations according to age.

Non-parametric testing showed there was no statistical significant difference between the two populations for the age group < 75 years and for the age group ≥ 75 years old ($p = 0.2363$ and $p = 0.1616$ respectively).

When we looked at the albumin levels in the fracture population 44 patients were included under the age of 75 years old. 79.55% of the patients had a deficiency compared to 80.59% of the patients (n = 103) 75 years and older (table VII). There was no statistical significant difference ($p = 0.8482$) in the albumin levels in the fracture population for the two age groups. For the reference population 109 patients were included in the younger than 75 years old age group when we looked at the albumin levels. 35.78% of the patients had a deficiency compared to 45.10% of the patients (n = 51) older than 75 years old (table VII). Non-parametric testing showed no statistical significant difference ($p = 0.1151$) in albumin levels in the reference population for the two age groups (figure 4).

DISCUSSION

Our results show that the majority of the patients, not yet receiving any form of vitamin D supplement therapy, admitted to our ward with either a hip or femur fracture, or for an elective hip arthroplasty have a vitamin D deficiency. A German study in 2012 showed that approximately 80% of the European population had a vitamin D bloodserum concentration below 30 ng/mL *(18)*, and an Indian study of orthopedic patients showed that more than 61% of the patients had a bloodserum level below 20ng/mL *(15)*. Our results are in line with

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these findings. In our fracture population there was no statistical significant difference in vitamin D levels between the months of the year with the most and the least hours of sunlight exposure. In the reference population there were significantly fewer vitamin D deficiencies in the months with the most hours of sunlight exposure. For both populations no statistical significant difference was shown in vitamin D and albumin levels for the patients under the age of 75 years and the patients over the age of 75 years and therefore age is not a good predictor for vitamin D deficiency.

Our results were recorded according to cut-off values set by the hospital's laboratory : vitamin D deficiency < 20ng/mL, calcium < 2.12 mmol/L and albumin < 29g/L. However, in literature the following cut off values most often used are : vitamin D deficiency < 20 ng/mL, hypocalcemia < 2.1 mmol/L and hypoalbuminemia < 35g/ L. There is no consensus on the exact definition of vitamin D deficiency or insufficiency *(11)*. According to The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), a minimal serum 25-hydroxyvitamin D level of 20 ng/mL should be maintained *(14)*. In elderly patients who have a higher risk of falling, the ESCEO recommends a minimum vitamin D level of 30 ng/mL *(14)*. An internationally recognized reference standard should be introduced.

If we had used a cut-off value of < 35g/L for albumin then more than 80.27% of the fracture population would have had a deficiency. Our results are actually an underestimation of the albumin deficiency in the population. One point of weakness in our study, however, is that the albumin level was collected postoperatively. This may have influenced the results as the albumin level may have been affected secondary to the patient's surgery. We must also consider the fact that a lower albumin level may also reflect existing co-morbidities rather than a single isolated cause *(4,17)*. A meta-analysis performed in 2017 found that patients with an albumin bloodserum level < 35 g/L had an almost 2.5 fold increased risk of surgical site infection, independent of the type of orthopedic surgery *(19)*. Hypoalbuminemia is a variable risk factor and simple interventions could potentially modify this *(16)*. The aim of this study however, was not to link albumin bloodserum levels to postoperative complications.

It has to be noted that our "reference group" is not a "healthy control group", but a real subgroup of orthopedic patients. It represents the "average", not the "healthy" patient in real life. Comorbidities and a patient's medical history were not taken into account. The same is applicable for the fracture population – comorbidities, current or previous therapy and medical history were not taken into account. No sex discrimination was made. A final limitation in our study is the missing data. Several patients received incomplete blood tests and therefore a systematic bias may have been introduced to the sample.

The main strength of this study is that it is, to the best of our knowledge, the first published, prospective study of vitamin D, calcium and albumin bloodserum levels in Belgian orthopedic patients including more than 341 patients.

The NGC 2009 guidelines do not advise all patients to be systematically screened for a vitamin D deficiency. They only recommend high risk patients to be screened such as those with chronic musculoskeletal pain, osteoporosis, rheumatoid arthritis, malabsorption syndromes, obesity, metabolic syndromes, and type II diabetes, cardiovascular disease, chronic kidney disease and hyperparathyroidism, depression, over 71 years of age, chronic use of corticosteroids, and a personal/social history of inadequate sun exposure *(5,6)*. Other guidelines state that routine serum testing or screening for a vitamin D deficiency is not recommended *(9)*, that universal testing is too expensive *(10)* and that supplementation without testing is advised *(12)*. The U.S. Preventive Services Recommendation Statement found no studies that evaluated the direct benefit of screening for vitamin D in adults *(11)*. In our hospital the cost for additional vitamin D, calcium and albumin bloodserum testing is between € 3-5 per patient.

Based on our findings we think it is justified to organize systematic vitamin D bloodserum level screening for all patients admitted to an orthopedic ward. If bloodserum levels are deficient (< 20 ng/L), therapy should be started. It might even be advocated to simply eliminate the screening and

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start all patients on supplement therapy. Due to the low cost of testing however, we will continue to screen systematically in order to avoid over- as well as undertreating our patients. The U.S. Preventive Services Recommendation Statement found adequate evidence that the harms of treatment of vitamin D deficiency are small to none *(11)*. Future studies should aim to prove whether or not systematic screening and treatment of vitamin D deficiencies improve clinical outcomes and reduce fracture risk in orthopedic patients. However, our results also show that a significant percentage of the population already under vitamin D supplement therapy still have a deficiency. Therefore, adequate supplement therapy in the correct doses must be given, though this goes beyond the scope of our study.

Garwe et al. claim that albumin bloodserum testing should be used as a prognostic tool to predict risk of in-hospital complications, particularly in the geriatric trauma patients *(7)*. We support this claim and recommend systematic screening for all hospitalized orthopedic patients, as well as nutritional advice and dietary counseling for all patients with an albumin bloodserum level below 29 g/L.

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