



## Vitamin D deficiency is associated with longer hospital stay and lower functional outcome after total knee arthroplasty

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High vitamin D deficiency prevalence has been found in hip and knee osteoarthritis, and a correlation between low vitamin D levels and worse functional outcome after hip arthroplasty was published before. Our goal was to examine the relation between vitamin D levels and outcome after knee arthroplasty on short and long term. In 138 patients with knee replacements preoperative vitamin D levels were recorded. 33 patients were vitamin D deficient (median 32 nmol/l, range 6-40 nmol/l) and 105 patients were vitamin D sufficient (median 65 nmol/l, range 41-177 nmol/l). After correction for confounders, vitamin D deficient patients had significant ( $p = 0.03$ ) longer hospital stay (+1.0 day, range 0.2-1.6 day), and significant ( $p = 0.04$ ) worse functional outcome also at long term follow up after eight years (WOMAC : +5.0, range 0.2-9.8). More research is needed to evaluate if rehabilitation and postoperative outcome can be improved by preoperative vitamin D supplementation.

**Keywords :** Total knee arthroplasty ; vitamin D deficiency ; functional outcome.

### INTRODUCTION

Osteoarthritis (OA) is characterized by loss of cartilage and subchondral bone changes, which can have a further influence on the progression of OA. (4,29) Besides the subchondral remodeling process and the capacity to respond to stress loading also a low bone density can affect progressive OA disease. (4) Sufficient levels of vitamin D are necessary

for adequate bone remodeling and cartilage metabolism.<sup>17</sup> Vitamin D deficiency has been shown to alter calcium metabolism and osteoblast activity, what may cause pain, muscular weakness, falls and knee OA progression. (2,17) Vitamin D plays a central role in calcium homeostasis and is mainly derived from exposure to sunlight, and from the diet. (17) The nutritional status of vitamin D is best reflected by the main circulating metabolite 25-hydroxyvitamin D3 (25(OH)D3) although the cut off point for vitamin D deficiency is still arbitrary. (17,29) Little sunlight exposure and low serum 25(OH)D3 levels are both associated with increased knee cartilage loss. (7,27) Especially in women with knee OA increased bone resorption has been found, which was consistent with metabolically more active subchondral bone. (12)

Vitamin D insufficiency and knee OA are both very common at a higher age. More than 12% of people over 55 years have symptomatic knee OA with radiographic degenerative changes. (6) Low levels of vitamin D have been reported in 22-36%

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of patients with hip OA, (10,18) and in patients with knee OA even up to 66%. (4) Increased cartilage loss assessed by radiograph or MRI has been reported in association with low vitamin D levels. (8) This may imply that achieving vitamin D sufficiency could prevent or slow down knee OA, (2) and could possibly improve the results after knee arthroplasty.

In a total hip replacement study a positive correlation between pre-operative vitamin D levels and post-operative Harris Hip scores has been published in the past. (21) A high prevalence of vitamin D deficiency in patients with osteoarthritis before total knee replacement was reported before. (13) In this study group the patients knee function and length of stay after total knee replacement was analyzed in relation to their pre-operative vitamin D levels. Our hypothesis was that vitamin D deficient patients would have a longer length of stay in hospital as well as lower post-operative knee scores both on the short and the long term.

## PATIENTS AND METHODS

Between December 2002 and December 2003 plasma 25(OH)D3 levels were measured from routine blood samples taken from patients in the pre-admission clinic before total knee replacement. Only Caucasian patients that were not taking any vitamin D medication were consented for 25(OH)D3 measurement by the I125 radioimmunoassay (Diasorin, Stillwater, Minnesota). The statement from the British scientific committee on nutrition as stated in their National Diet and Nutrition Survey from 2007 was used to make an arbitrary division of vitamin D deficiency ( $\leq 40$  nmol/l 25(OH)D3) and sufficient vitamin D levels ( $>40$  nmol/l 25(OH)D3). In total 138 patients were included in the study. All patients received a cemented primary knee arthroplasty (138 arthroplasties). From all 138 patients preoperative 25(OH)D3 levels were available. Additionally, age, sex and comorbidity as classified by the American Society of Anaesthesiologists (ASA grade) were documented.

Outcome parameters were the total length of hospital stay and knee function. The length of hospital stay was recorded for all 138 patients. 123 patients were seen by the orthopaedic research

nurse for pre-operative assessment of their knee function by the Western Ontario McMasters University (WOMAC) questionnaire which is a subjective scoring instrument. Functional outcome was measured again six months (104 patients) and eight years (68 patients) after the operation by the same research nurse.

All the total knee replacements were performed by the same orthopaedic consultant or by a senior registrar under his supervision. For the knee arthroplasty a cemented Triathlon posterior stabilized component (Stryker, Kalamazoo, Michigan) was used with polyethylene fixed bearing and patellar resurfacing. A standard anterior midline incision was used with a medial parapatellar arthrotomy for exposure of the joint.

Data were collected prospectively, however, due to the retrospective nature of the analysis a power analysis was not conducted. The Kolmogorov-Smirnov test was used to test normality. Levene's test was used to test for equality of variances. Independent t-tests and the Mann-Whitney Rank Sum test were used for comparison of demographics between vitamin D deficient patients and vitamin D sufficient patients.

Univariate analysis was used for estimating the relation between preoperative vitamin D serum concentrations and outcome parameters. Total length of hospital stay and the WOMAC score were used as dependent variables. In order to meet the prerequisites for univariate analysis, a log transformation was conducted for days to discharge. Serum vitamin D concentration was used as an independent variable (covariate). For univariate analysis of the relation between preoperative serum vitamin D concentration and the total length of hospital stay, age (covariate), sex (fixed factor) and ASA classification (fixed factor) were added as independent variables to correct for confounding. For univariate analysis of the relation between preoperative serum vitamin D concentration and postoperative function (WOMAC), the follow-up time was introduced as an extra independent variable (covariate). Analysis was performed with SPSS 20 and Sigstastat 3.5 (SPSS Inc and Systat respectively, Chicago, Illinois, US). Results were expressed as mean (standard deviation), median

(range), box-plot (median, 25th and 75th percentile, extremes) and nanomol per liter (nmol/l).

## RESULTS

Of the 138 patients that were analyzed, 33 patients were diagnosed as vitamin D deficient ( $\leq 40$  nmol/l) and 105 patients as vitamin D sufficient ( $> 40$  nmol/l). Mean age, ASA score, sex, and follow up time were comparable between vitamin D deficient and vitamin D sufficient patients (Table 1).

### *Relation between length of hospital stay and pre-operative vitamin D level*

Patients in both groups were discharged after a median stay of 7 days, but there was a difference in range between the vitamin D deficient group (range : 2-28 days) and the vitamin D sufficient group (range : 2-19 days) respectively ( $p=0.31$ ). After correction for sex and age in univariate analysis, lower vitamin D concentrations ( $p = 0.028$ ) and higher age ( $p = 0.004$ ) were significantly associated with a longer stay in hospital (Table 2).

Table I. — Patient demographics of vitamin D deficient versus vitamin D sufficient patients.

Parameter	vit D $\leq 40$ nmol/l	vit D $> 40$ nmol/l	difference (95% CI)	p
Vitamin D (nmol/l)	32 (range: 6-40)	65 (range: 41-177)	43 (n.a.)	$< 0.001$
Age	69.9 years	72.8 years	3 (-1 to +6)	0.10
ASA score	2 (range: 1-3)	2 (range:1-3)	0 (n.a.)	0.98
% Female (F:M)	61% (20:13)	58% (61:44)	3 (-17 to +22)	0.96

Table II. — Relation between length of hospital stay and preoperative serum vitamin D concentration, corrected for potential confounders: lower vitamin D level and higher age are associated with longer length of stay.

Dependent variable: Length of stay	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Vitamin D	-,001	,001	-2,226	,028	-,003	,000
Age	,006	,002	2,967	,004	,002	,010
sex=female	,054	,034	1,595	,113	-,013	,120
sex=male	0 <sup>a</sup>	.	.	.	.	.
ASA=1	-,066	,061	-1,088	,279	-,186	,054
ASA=2	-,071	,049	-1,452	,149	-,167	,026

### *Association between functional outcome (WOMAC score) and pre-operative vitamin D level*

Pre-operatively the mean WOMAC scores in the vitamin D deficient group and the vitamin D sufficient group were 77 (20) and 75 (17) respectively (95% CI : -6 to 9,  $p = 0.73$ ). At 6 months follow-up the median WOMAC scores were 39 (range : 29-100) and 38 (range : 24-102) respectively ( $p=0.20$ ). After 8 years follow-up the median WOMAC scores

changed to 49 (range : 28-94) and 38 (range : 24-120) respectively ( $p = 0.33$ ).

With univariate regression analysis (correcting for age, sex, ASA grade and follow-up time) a significant association was found between vitamin D serum concentration and post-operative WOMAC scores. A worse WOMAC score was significantly ( $p=0.040$ ) associated with lower pre-operative vitamin D serum concentration (3). Also higher age, female sex and longer follow up time were related to lower WOMAC outcome scores as expected.

Table III. — Association between lower preoperative serum vitamin D concentration and worse WOMAC outcome score, corrected for potential confounders and follow-up time. Also higher age and female sex were associated with significant lower functional outcome scores.

Dependent variable: WOMAC score	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Vitamin D	-,126	,061	-2,064	,040	-,245	-,006
Age	-,430	,212	-2,023	,044	-,848	-,011
Female sex	10,839	3,247	3,338	,001	4,436	17,242
FU time	-2,501	,525	-4,765	,001	-3,537	-1,466
ASA=1	-8,415	5,757	-1,462	,145	-19,768	2,939
ASA=2	-1,603	4,970	-,322	,747	-11,404	8,199

*Subgroup analysis in specific gender (female), higher age (80), and lower vitamin D status (30 nmol/l)*

The parameters from the univariate analyses were used to calculate the potential effects of vitamin D concentration, corrected for age and sex, on total length of hospital stay (days) and postoperative knee function (WOMAC 8 years post-operatively). In order to compare the magnitude of the effect of preoperative vitamin D concentration on the outcome measurements with the effect of other patient dependent variables, the specific effect of age and sex were also calculated as these appeared to have significant influence on outcome as well. The corresponding univariate parameters were used together with clinically relevant differences in vitamin D concentration (low : 30 mmol/l, compared to high : 70 mmol/l), age (high : 80 years, compared to low : 50 years) and sex (female compared to male). A low pre-operative serum vitamin D concentration (30 mmol/l) resulted in a significant +1.0 day longer length of stay in hospital ( $p = 0.03$ ). Also older age (80 years) significantly prolonged stay by +2.7 days ( $p = 0.004$ ) and female sex +0.8 day, but not significantly ( $p = 0.11$ ). Patients with a low preoperative vitamin D concentration had a worse WOMAC scores (+5.0) compared to patients with a normal preoperative vitamin D concentration at follow up. Female patients also had significantly worse WOMAC scores with +10.7 ( $p = 0.001$ ). The lower WOMAC score -11 ( $p = 0.04$ ) for older patients represents a

better postoperative subjective functional outcome compared to younger patients. (Table 4).

## DISCUSSION

It is well known that the pre-operative knee function is strongly related to the functional outcome after total knee replacement. (9) It has also been reported that there is a relationship between low vitamin D levels and OA of the knee. (8,11,12) A recent publication described the negative effect of pre-operative hypovitaminosis D on post-operative pain scores as well. (15) As a low dietary vitamin D intake increases the risk of progression of knee OA, improving the vitamin D status in the elderly may protect against development and worsening of knee OA. (2) A randomized controlled trial in elderly women did show that vitamin D supplementation improved functionality with regards to walking speed and endurance. (5) A twelve month clinical trial in elderly women after total hip replacement showed improvement in outcome with daily calcitonin nasal spray. The functional status of the patients was significantly improved and there was a reduction in bone turnover, loss of bone density and pain. (24) The pre-operative vitamin D status may therefore be related to post-operative knee function as well, and achieving vitamin D sufficiency can possibly improve outcome after total knee replacement.

Low plasma 25(OH)D3 levels are also associated with a range of inflammatory diseases, and have been shown to be decreased after total knee replacement. (26) This decrease in Vitamin D levels after knee

Table IV. — Calculated differences (95% CI) in specific subgroups based on univariate analysis of length of stay and clinical outcome at follow up 8 years post-operatively. Lower vitamin D status (30 nmol/l) and higher age (80 years) account for a significant longer length of stay. Low vitamin D status and female sex both show a lower functional outcome on long term follow up as well.

Variable	Length of stay (days)	p value	WOMAC at 8 years	p value
Vitamin D: low	+1.0 (0.2 to 1.6)	p = 0.03	+5.0 (0.2 to 9.8)	p = 0.04
Age: high	+2.7 (0.5 to 8.4)	p = 0.004	-11 (-22.8 to 1.7)	p = 0.04
Sex: female	+0.8 (-0.2 to 2.0)	p = 0.11	+10.7 (4.3 to 17.0)	p = 0.001

arthroplasty appears to be persistent for several months, and may also warrant further research into the relationship between peri-operative vitamin D levels and functional outcome after total knee replacement.

Genetic studies have shown that specific Vitamin 25(OH)D3 Receptors (VDR) are mostly present in the bone and gastrointestinal tract, where calcium flow is very active.<sup>(16)</sup> The VDR genotype has been shown to be associated with radiographic osteoarthritis at the knee.<sup>(28)</sup> The VDR also plays a role in the biological cascade of events initiated by particulate wear debris and bacterial infection, what can result in periprosthetic bone loss around total hip replacements.<sup>(19)</sup> The genetic variation in allele polymorphism may dictate the response to such stimuli,<sup>(22)</sup> what ultimately can lead to prosthetic loosening. VDR expression has been seen in muscular biopsy specimens of all orthopaedic patients as well. Older age is significantly associated with decreased VDR expression independent of 25(OH)D3 levels.<sup>(3)</sup> This may suggest that the age related decline in muscle strength could be partly explained by decreased VDR expression. Further studies are necessary though to see whether VDR expression can be increased by vitamin D supplementation in order to prevent periprosthetic bone loss or loosening, and improve outcome of arthroplasty.

Within the same group of patients with advanced knee OA we have reported a vitamin D deficiency prevalence of 24% comparable to previous studies.<sup>13</sup> Our goal was to investigate the relation between pre-operative vitamin D levels and outcome after total knee replacement. Univariate analysis in this study, correcting for age, sex and comorbidity, has shown

for the first time a statistically significant association between preoperative vitamin D deficiency and lower functional outcome on short and long term. The disease specific WOMAC questionnaire was used as an outcome measurement.

The finding in our study that higher age lengthens hospital stay was previously described,<sup>(25)</sup> and also published in a prediction model for length of stay after total knee replacement as well.<sup>(23)</sup> Besides diet and seasonal influences there are several confounding factors that can influence pre-operative vitamin D levels though, that were not accounted for.<sup>(20)</sup> For instance, lower body mass index and bone mineral density can be related to vitamin D deficiency<sup>(30)</sup>. However, in this study no standard bone scintigraphy was done. With regards to the post-operative functional outcome there are some limitations as well. Firstly, functional assessment by WOMAC scores can be quite subjective and was not performed at all follow-up moments in every patient. Secondly, the association between hip and knee OA was not taken into account specifically with regard to the post-operative outcome assessment.<sup>(14)</sup> Also coexisting disease in the lumbar spine and contralateral knee osteoarthritis were not documented in detail during this study. A recent publication showed though that these factors are associated with poorer physical function after total knee replacement as well.<sup>(1)</sup> This study has shown the association between vitamin D deficiency and longer hospital stay with lower functional outcome after total knee replacement also on long term follow up. Further research into vitamin D supplementation is necessary as it may be able to improve functional outcome after total knee replacement on short and long term.

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