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Vitamin D deficiency adversely affects  
early postoperative functional outcomes  
after total knee arthroplasty

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Vitamin D deficiency adversely affects  
early postoperative functional outcomes  
after total knee arthroplasty

Directed by Professor Seong Hwan Moon

The Master's Thesis submitted to the Department of  
Medicine, the Graduate School of Yonsei University  
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## ABSTRACT

Vitamin D deficiency adversely affects early postoperative functional outcomes after total knee arthroplasty

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### **Introduction**

Vitamin D has received considerable attention in recent years owing to the increasing evidence of its importance in muscle function and physical performance. The present study attempted to determine whether patients with low serum vitamin D levels had impairment in early functional outcomes following total knee arthroplasty (TKA).

### **Materials and Methods**

This was a prospective cohort study that included 92 patients. Patients were divided into two groups according to their vitamin D levels as assessed at the preoperative visit: (1) vitamin D deficient group, serum 25-hydroxyvitamin D<sub>3</sub> (25(OH)D) levels < 12 ng/mL; (2) vitamin D non-deficient group, serum 25(OH)D levels ≥ 12 ng/mL. American Knee Society Score (KSS) and four other



performance tests including the Alternative Step Test (AST), Six Meter Walk Test (SMT), Sit To Stand Test (STS), and Timed Up and Go Test (TUGT) were used for assessment of postoperative function. All assessments were performed one day before and three months after TKA.

## **Results**

Of the 92 patients included in the study, 87 patients performed all required assessments. The mean postoperative functional KSS was significantly lesser in the vitamin D deficient group than in the vitamin D non-deficient group (67.2 vs. 73.4,  $p = 0.031$ ). The mean values of time taken for postoperative AST (16.6 vs. 14.6,  $p = 0.033$ ) and SMT (8.8 vs. 7.7,  $p = 0.012$ ) were significantly longer in the vitamin D deficient group than in the vitamin D non-deficient group. Postoperative STS and TUGT demonstrated higher values for mean time taken in the vitamin D deficient group than in the vitamin D non-deficient group, but these were not statistically significant (13.6 vs. 12.4, not significant (n.s.); 12.7 vs. 11.7, n.s., respectively).

## **Conclusions**

Early postoperative functional outcomes following TKA appear to be adversely affected by vitamin D deficiency.

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Key words: Total knee arthroplasty, Vitamin D, Functional outcomes, American Knee Society Score, Performance tests

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## **I. INTRODUCTION**

Total knee arthroplasty (TKA) is a commonly performed procedure for end-stage osteoarthritis (OA) of knee. Although TKA results in significant pain relief and improvement in quality of life<sup>1</sup>, it is associated with substantial muscle and bone damage, and prolonged recovery. Reducing muscle injury is an important element in facilitating postoperative recovery following TKA.

Vitamin D has received considerable attention in recent years owing to increasing evidence of its important role in many tissues including skeletal muscle. Vitamin D is essential for calcium homeostasis and bone turnover<sup>2</sup>, and has a positive effect on the improvement of muscle function<sup>3, 4</sup>. Although a clear

mechanism is unknown, vitamin D is also known to be associated with extraskeletal diseases, such as cardiovascular diseases, diabetes, auto-immune diseases, and cancer<sup>5,6</sup>. Nevertheless, vitamin D deficiency is a common problem affecting approximately one billion people worldwide<sup>7,8</sup>, with elderly population affected more frequently<sup>9,10</sup>.

Evidence from several studies demonstrated an association between vitamin D status, and skeletal muscle function and physical performance<sup>11-13</sup>, while other studies found no such association<sup>14</sup>. The role of vitamin D and its influence on functional recovery following total knee arthroplasty (TKA) are not clearly established. There is a study demonstrated no association between vitamin D status and postoperative outcomes after TKA<sup>15</sup>. However, in this study, there was lack of evaluation for physical function.

Vitamin D could be a potentially important factor in improving postoperative physical function following TKA, considering its effect on musculoskeletal system. The objective of the present study was to investigate the effects of vitamin D on early functional outcomes after TKA. We hypothesized that early functional outcomes following TKA would be impaired in patients with low serum vitamin D levels.

## II. MATERIALS AND METHODS

### Data Collection

This was a single-centre prospective cohort study. All patients diagnosed as primary OA of the knee and scheduled for unilateral primary TKA were eligible for inclusion in the study. The exclusion criteria were patients who had (1) postoperative complications that would change the rehabilitation plan; (2) symptomatic spinal degenerative disease or neuropathy; (3) symptomatic severe OA of the hip or ankle (Kellgren Lawrence grade 3 or more); (4) evidence of metabolic bone disease (hypo- or hyperparathyroidism, chronic renal disease); (5) psychiatric or neurodegenerative disorders; and (6) history of drug intakes including vitamin D, calcium, or bisphosphonates prior to surgery. All surgeries were performed by one senior author (WSL) by using a mid-vastus approach. A cemented and posterior cruciate ligament substituting prostheses was used in all cases.

From October 2014 to May 2015, 92 out of 120 patients, assessed for eligibility for inclusion in the study, were enrolled. Twenty-eight patients were excluded for various reasons, including refusal to participate ( $n = 14$ ); history of drug use including vitamin D, calcium or bisphosphonate ( $n = 7$ ); symptomatic spinal stenosis ( $n = 5$ ); postoperative complications including surgical site infection ( $n = 1$ ); and pulmonary thromboembolism ( $n = 1$ ). Among the 92 patients enrolled, 5 patients missed the appointment at the third-postoperative

month. Thus, only 87 patients performed all required assessments.

Age, gender, body mass index (BMI), and side of surgery were recorded. The American Society of Anesthesiologists (ASA) score was used as a measure of comorbidity<sup>16</sup>.

Blood samples were obtained at the preoperative visit. Serum 25-hydroxyvitamin D<sub>3</sub> (25(OH)D) levels were measured by I<sup>125</sup> radioimmunoassay (DIAsource ImmunoAssays SA, Louvain-la-Neuve, Belgium). 25(OH)D is commonly used to determine vitamin D status since it is the principle circulating metabolite, and its plasma level best reflects the nutritional status of a patients with respect to vitamin D. The Institute of Medicine, which proposes dietary reference intakes for calcium and vitamin D, defines adequate levels of 25(OH)D as 20 ng/mL, deficiency as levels less than 12 ng/mL, and insufficiency as levels between 12 and 20 ng/mL<sup>17</sup>. Patients were divided into two groups based on serum levels of 25(OH)D: (1) vitamin D deficient group, serum 25(OH)D levels < 12 ng/mL; (2) vitamin D non-deficient group, serum 25(OH)D levels ≥ 12 ng/mL. Serum calcium, albumin, and parathyroid hormone levels were also measured as part of the metabolic panel.

American Knee Society Score (KSS) and four other performance tests were used for assessment of postoperative outcomes. All assessments were performed one day before and three months after TKA. KSS is a well-established scoring system and has been widely used in large studies<sup>18, 19</sup>, institutional databases and

registries. It is subdivided into a score that rates clinical evaluation of the knee joint itself (clinical KSS) and another score that rates the functional ability to walk and climb stairs (functional KSS)<sup>20</sup>. The clinical KSS includes pain, stability, and range of motion (ROM) as the main parameters, with appropriate deductions for flexion contractures, extension lag, and malalignment. A well aligned knee with no pain, 125° ROM, and negligible anteroposterior or mediolateral instability is given the maximum score of 100 points on clinical KSS. The functional KSS, includes walking distance and stair climbing as the main parameters, with deduction for the use of a walking aid. The maximum score for functional KSS is also 100 points, for a patient who is able to walk an unlimited distance and ascend and descend stairs normally.

The four performance tests included the Alternative Step Test (AST), Six Meter Walk Test (SMT), Sit To Stand Test (STS) and Timed Up and Go Test (TUGT). These four tests were validated by previous studies<sup>21-27</sup>. AST involves weight shifting and provides a measure of lateral instability. The test is performed by alternatively placing the entire left and right feet as fast as possible onto a step that was 18-cm high and 40-cm deep. The test measure was the time taken to complete eight steps. For SMT, the time taken to walk a distance of six meters was measured. Subjects were asked to walk along a corridor at their normal walking speed. An added distance of two meters at either end of the six meter stretch ensured a constant speed over the designated distance. For STS, subjects

were asked to rise from a chair without armrests with their arms folded, as fast as possible. The time taken to complete five stands, from the initial seated position to the final seated position was measured. For TUGT, patients were instructed to rise from a standard chair, walk at a normal pace to a mark three meters away, and return to the sitting position with their backs against the chair. Patients were permitted to use their arms when rising from and returning to a seated position. A stopwatch was used to measure the time to complete activities to the nearest tenth of a second. All patients were assessed by the same observer (HJC).

The present study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (3-2013-0068) and informed consent was obtained from all patients who participated in the study.

### **Statistical analysis**

To establish test-retest reliability of the four performance tests in the current study, a random sample of 20 patients in each group was selected. Intraclass correlation coefficients (ICCs) were used to describe the measures' test-retest reliability. Repeated measurements with the four tests showed high ICC (ICC = 0.89 for AST, ICC = 0.87 for SMT, ICC = 0.91 for STS, and ICC = 0.86 for TUGT).

Continuous data were presented as mean  $\pm$  standard deviation (SD) for normally distributed variables and as median and interquartile ranges for variables

that were not normally distributed. Data were analysed using independent samples *t*-test or Mann-Whitney *U* test. Categorical variables were presented as frequencies and percentages, and compared using Chi-square test. Statistical significance was set as *p* value < 0.05. All analyses were conducted using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

Sample size calculation was based on the difference in the primary outcome (functional KSS) between the two groups and was performed by using PASS software, version 12.0 (NCSS, Utah, USA). A review of sixty patients who had undergone a primary unilateral total knee arthroplasty at our institution from January to June 2014 showed that the mean functional KSS at the third postoperative month was  $64.3 \pm 12.3$  in vitamin D deficient group and  $72.3 \pm 14.5$  in vitamin D non-deficient group. Based on this data, the expected effect size was determined as 0.60. The sample size was calculated as 45 patients in each group, for an acceptable alpha value of 0.05, power of 0.8 and to account for a 20% drop-out rate.



### III. RESULTS

There were no differences in the study population with respect to demographic data and clinical characteristics such as age, gender, BMI, side of surgery, and ASA score (Table 1). Apart from the expected difference in 25(OH)D levels between the two groups, there were no significant differences between them in their serum levels of calcium, albumin, and parathyroid hormone levels (Table 2).

The preoperative measurements including clinical KSS, functional KSS and the four performance tests demonstrated similar values for the two study groups (Table 3).

There was no difference between the groups in terms of postoperative clinical KSS. The mean postoperative functional KSS was significantly lesser in the vitamin D deficient group than in the vitamin D non-deficient group (67.2 vs. 73.4,  $p = 0.031$ ). The mean values of time taken for postoperative AST (16.6 vs. 14.6 s,  $p = 0.033$ ) and SMT (8.8 vs. 7.7 s,  $p = 0.012$ ) were significantly longer in the vitamin D deficient group than in the vitamin D non-deficient group. Postoperative STS (13.6 vs. 12.4 s, not significant (n.s.)) and TUGT (12.7 vs. 11.7 s, n.s.) demonstrated higher values for mean time taken in the vitamin D deficient group than in the vitamin D non-deficient group, but these were not statistically significant (Table 4).

**Table 1. Demographic and clinical characteristics**

Variables	Vitamin D deficient group (n = 43)	Vitamin D non-deficient group (n = 44)	p-value
Mean age, year	70.7 ± 6.8	72.4 ± 6.2	n.s.
Female sex, n (%)	39 (90.7%)	39 (88.6%)	n.s.
BMI, kg/m <sup>2</sup>	25.7 ± 4.1	25.3 ± 2.7	n.s.
Right side, n (%)	18 (41.9%)	21 (47.7%)	n.s.
ASA score, n (%)			n.s.
1	2 (4.7%)	7 (15.9%)	
2	19 (44.2%)	14 (31.8%)	
3	22 (51.2%)	23 (52.3%)	

Continuous data are shown as mean ± standard deviation and categorical variables are presented as frequencies and percentages.

n.s. not significant

ASA American Society of Anesthesiologists

**Table 2. Baseline laboratory tests**

Variables	Vitamin D deficient group (n = 43)	Vitamin D non-deficient group (n = 44)	p-value
Serum 25(OH)D ng/mL	9.1 (6.8-10.8)	18.3 (15.6-26.0)	< 0.001*
Serum PTH, pg/mL	38.4 ± 11.6	34.2 ± 11.8	n.s.
Serum calcium, mg/dL	8.8 ± 0.3	8.9 ± 0.5	n.s.
Serum albumin, g/dL	4.1 (3.9-4.3)	4.1 (3.7-4.3)	n.s.

Data are shown as mean ± standard deviation for normally distributed variables and as median and interquartile ranges for variables that were not normally distributed.

\* significant difference between two groups, n.s. not significant

25(OH)D 25-hydroxyvitamin D<sub>3</sub>, PTH parathyroid hormone

**Table 3. Preoperative measurements**

	Vitamin D deficient group (n = 43)	Vitamin D non-deficient group (n = 44)	p-value
Clinical KSS	56.2 ± 10.1	58.9 ± 13.6	n.s.
Functional KSS	53.5 ± 12.8	54.5 ± 8.3	n.s.
AST (s)	21.2 ± 5.7	21.1 ± 5.2	n.s.
SMT (s)	11.9 ± 3.3	12.0 ± 3.5	n.s.
STS (s)	15.1 ± 3.1	14.2 ± 2.5	n.s.
TUGT (s)	12.6 (10.6-16.5)	14.0 (11.0-16.4)	n.s.

Data are shown as mean ± standard deviation for normally distributed variables and as median and interquartile ranges for variables that were not normally distributed.

n.s. not significant

KSS American Knee Society Score, AST Alternative Step Test, SMT Six Meter Walk Test, STS Sit to Stand Test, TUGT Timed Up and Go Test

**Table 4. Postoperative measurements**

	Vitamin D deficient group (n = 43)	Vitamin D non-deficient group (n = 44)	p-value
Clinical KSS	83.2 ± 9.0	85.3 ± 8.5	n.s.
Functional KSS	67.2 ± 12.0	73.4 ± 14.5	0.031*
AST (s)	16.6 ± 5.1	14.6 ± 3.7	0.033*
SMT (s)	8.8 ± 2.3	7.7 ± 1.6	0.012*
STS (s)	13.6 ± 3.6	12.4 ± 2.6	n.s.
TUGT (s)	12.7 ± 4.0	11.7 ± 2.8	n.s.

Data are shown as mean ± standard deviation for normally distributed variables and as median and interquartile ranges for variables that were not normally distributed.

\* significant difference between two groups, n.s. not significant

KSS American Knee Society Score, AST Alternative Step Test, SMT Six Meter Walk Test, STS Sit to Stand Test, TUGT Timed Up and Go Test

## IV. DISCUSSION

The most important finding of the present study was that early postoperative outcomes following TKA were affected by patients' preoperative vitamin D status, and those in the vitamin D deficient group had significantly poorer postoperative outcomes.

Recent evidence suggests that vitamin D deficiency is associated with the development and progression of OA, though the underlying pathophysiology is unclear<sup>28</sup>. In addition, studies have also reported vitamin D deficiency in a relatively high proportion of patients with OA of hip or knee<sup>29-31</sup>. However, since there is lack of consensus on the cut-off levels to define the normal serum values of vitamin D, the actual prevalence of suboptimal levels (insufficiency or deficiency) is not known with certainty<sup>32</sup>. The Institute of Medicine concluded that serum 25(OH)D levels of 20 ng/mL (50 nmol/L) are sufficient to meet the needs of 97.5% of population<sup>17</sup>, while the International Osteoporosis Foundation as well as Osteoporosis Canada consider 30ng/mL to be the lowest normal value based on the correlation between vitamin D levels, parathyroid hormone response, and calcium reabsorption<sup>33,34</sup>. Consequently, the lack of a standard definition makes it difficult to compare the results of different studies.

There is increasing evidence, especially during the past several decades, of the important role played by vitamin D in skeletal muscle pathophysiology. Muscle biopsies in adults with profound vitamin D deficiency demonstrate

predominantly type II muscle fiber atrophy<sup>35</sup>. In addition, vitamin D supplementation is associated with increased diameter and percentage of type II muscle<sup>36</sup>. The identification of the vitamin D receptor (VDR) on the surface of muscle cells provided further evidence supporting a direct role played by the vitamin in muscle tissue structure and function<sup>37</sup>. Studies over the last two decades are identifying genomic effects of 1,25(OH)<sub>2</sub>D, which are related to the synthesis of new proteins affecting muscle cell contractility, proliferation, and differentiation<sup>37,38</sup>. In addition, scientists are gradually constructing non-genomic pathways of 1,25(OH)<sub>2</sub>D activity in muscle cells that potentially impact muscle contraction and muscle cell development<sup>39</sup>. Certain epidemiologic studies demonstrated a positive association between vitamin D status and physical performance<sup>11-13</sup>, while other studies found no such association<sup>14</sup>. Because TKA results in substantial injury to extensor mechanism of the knee, it is pertinent to evaluate the association between serum vitamin D levels and functional recovery following TKA.

In a recent study correlating vitamin D levels with postoperative outcomes in patients undergoing TKA, patients with vitamin D deficiency (defined as serum 25(OH)D < 16 ng/mL) had lower preoperative KSS (31.5 vs. 37.1, p=0.047) when compared to patients without deficiency<sup>15</sup>. Although the postoperative KSS was also lower in patients with vitamin D deficiency, the difference between the two groups was not statistically significant (74.6 vs 80.4, n.s.). Thus, an association

between vitamin D deficiency and postoperative functional status was not demonstrated in this study. However, in this study, KSS was not distinguished as clinical or functional.

Our study focused on the functional recovery following TKA and demonstrated that patients in the vitamin D deficient group had significantly poorer postoperative outcomes as assessed by functional KSS, AST, and SMT. STS and TUGT also demonstrated higher values for mean time taken in the vitamin D deficient group, though these were not statistically significant. Our data clearly demonstrated that vitamin D deficiency adversely affected early postoperative outcomes following TKA. Since vitamin D deficiency can usually be corrected by 6 weeks of oral vitamin D supplementation<sup>40-42</sup>, preoperative vitamin D supplementation may be considered for patients with vitamin D deficiency, as a measure to improve postoperative outcomes.

In our study, there was no association demonstrated between vitamin D deficiency and other baseline patient characteristics (age, sex, BMI, comorbidities), while a direct association was demonstrated in several other studies<sup>43-46</sup>. In addition, both groups in our study were comparable in terms of all preoperative measurements including KSS and the four performance tests. Our results are in contrast to evidence in literature suggesting a positive association between vitamin D status and physical performance<sup>11-13</sup>. A possible explanation for our findings may be related to pain. End-stage OA of knee can cause



intolerable pain and subsequent obstacle of daily life. Therefore, the impact of pain could overwhelm the effect of vitamin D in patients scheduled for TKA.

The current study has several limitations. First, the follow-up period was limited to the first 3 months following surgery. Although we assumed that low vitamin D levels would impair early functional results following TKA, longer follow-up is essential to understand the effects of vitamin D deficiency on postoperative function. Second, our study did not anticipate a change in vitamin D status after surgery. Despite restricting intake of vitamin D supplements, such a change is possible owing to several factors, including increased outdoor activity or nutritional intake. Such a change in vitamin D status may have affected the outcomes after TKA. Third, there was lack of consideration about other factors that could influence physical performance. Although ASA score was used to assess comorbidity, other factors including cardiac disease, nutritional status and preoperative level of fitness may have influenced the functional outcomes. Another limitation is related to the performance tests that used by us. There are many performance-based tests available, and the most appropriate test for assessing functional outcomes of TKA is yet to be identified.

Despite these limitations, our study provides important information regarding the role of vitamin D in functional outcomes following TKA. We found a fairly consistent association between vitamin D deficiency and poorer functional outcomes following TKA.

## V. CONCLUSION

In the current study, early postoperative functional outcomes following TKA appear to be adversely affected by vitamin D deficiency. These findings indicate that surgeons should confirm vitamin D status before performing TKA and consider preoperative vitamin D supplementation for patients with vitamin D deficiency.

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ABSTRACT (IN KOREAN)

비타민 D 결핍은 인공슬관절치환술 후 초기 기능적 결과에 부정적인 영향을 미친다.

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서론

근기능과 육체적 활동에 있어서 비타민 D의 중요성을 밝힌 증거가 많아지면서, 비타민 D는 최근 큰 주목을 받고 있다. 이 연구에서는 비타민 D 결핍이 있는 환자들이 인공슬관절치환술 후 초기 기능적 결과가 더 떨어지는지를 알아보고자 하였다.

방법

이 연구는 전향적 코호트 연구로서 92명의 환자들을 대상으로 진행하였다. 환자들은 수술전 검사에 따라서 2개의 군으로 배정되었는데, 수술전 혈중 25-수산화비타민 D 농도가 12 ng/mL 미만인 경우 비타민 D 결핍군으로 정의하였고 12 ng/mL 이상인 경우에는 비타민 D 비결핍군으로 정의하였다. 수술후 결과를 평가하기 위해서 미국 슬관절학회 점수, Alternative step test (AST), Six meter walk test (SMT), Sit to stand test (STS), Timed up and go test

(TUGT)를 사용하였다. 모든 평가는 수술 하루 전과 수술 후 3개월째에 시행되었다.

## 결과

전체 92명중에서 87명의 환자들이 모든 평가를 시행받았다. 수술 후 평균 미국 슬관절학회 기능점수는 비타민 D 결핍군이 비타민 D 비결핍군에 비해서 통계적으로 유의하게 더 낮았다(67.2 vs. 73.4,  $p = 0.031$ ). 수술 후 AST (16.6 vs. 14.6,  $p = 0.033$ ), SMT (8.8 vs. 7.7,  $p = 0.012$ )를 완료하는데 걸린 평균시간은 비타민 D 결핍군이 비타민 D 비결핍군에 비해서 통계적으로 유의하게 더 길었다. 수술 후 STS, TUGT를 마치는데 걸린 평균시간은 비타민 D 비결핍군과 비교했을 때 비타민 D 결핍군에서 더 오래 걸렸으나, 통계적으로 유의한 차이는 없었다 (13.6 vs. 12.4,  $p = n.s.$ ; 12.7 vs. 11.7,  $p = n.s.$ ).

## 결론

본 연구에 따르면 인공슬관절 치환술 후 초기 기능적 결과는 비타민 D 결핍에 부정적인 영향을 미치는 것으로 사료된다.

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핵심되는 말 : 인공슬관절 치환술, 비타민 D, 기능적 결과, 미국 슬관절학회 점수, 행동 검사