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Effect of Vitamin D Deficiency on Periprosthetic Joint Infection and Complications after Primary Total Joint Arthroplasty

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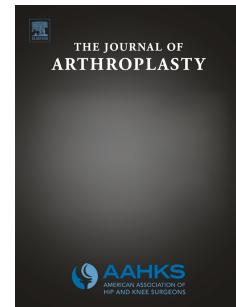
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Declarations

Conflicting interests

The authors declare that they have no competing interests.

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Abstract

Introduction

Vitamin D deficiency is a global problem, and 13 to 75% of patients undergoing total joint arthroplasty (TJA) have vitamin D deficiency. Several studies have shown that low preoperative vitamin D levels may increase the risk of postoperative complications, including periprosthetic joint infection (PJI), in patients undergoing primary TJA. However, most of the studies are underpowered. This study aimed to investigate the relationship between vitamin D deficiency and surgical and medical complications after primary TJA, with a specific focus on PJI.

Methods

Prospectively collected institutional multicenter arthroplasty databases were reviewed to identify patients who underwent primary total knee and hip arthroplasty between 2019 and 2022. The study group was defined as patients whose vitamin D level is < 30 ng/dl and who received a single oral dose of 7.5 mg (300,000 IU) D3 within two weeks before index surgery ($n = 488$; mean age 63 years). Patients in the control group were those whose preoperative vitamin D levels were unknown and who did not receive vitamin D supplementation ($n = 592$, mean age 66). Demographics, comorbidities, and 90-day postoperative surgical and medical complications were recorded. The groups were compared regarding 90-day medical and surgical complications, including PJI, mortality, and readmission rates.

Results

The total number of complications (8.6 and 4.3%; respectively; $P = 0.005$), superficial wound infection (2.5 and 0.2%, respectively; $P < 0.001$), and postoperative cellulitis (2.2 and 0% respectively; $P < 0.001$) were

statistically significantly higher in the patient group who did not receive vitamin D supplementation. However, 90-day mortality ($P = 0.524$), PJI ($P = 0.23$), and readmission rate ($P = 0.683$) were similar between the groups.

Conclusion

This study demonstrated that preoperative optimization of vitamin D levels may be beneficial in reducing postoperative complications, including superficial wound infection and postoperative cellulitis. Administering an oral 300,000 U single-dose vitamin D regimen to correct vitamin D deficiency can positively impact outcomes following primary TJA.

Keywords

D vitamin ; deficiency ; supplementation ; superficial wound problems ; periprosthetic joint infection

Introduction

Vitamin D is essential for the maintenance of bone health, muscle strength, and overall musculoskeletal function. Its impact extends beyond bone mineralization, influencing calcium regulation, muscle strength, and the prevention of musculoskeletal disorders[1,2]. However, hypovitaminosis D, or vitamin D deficiency remain a widespread global health concern, affecting approximately one billion individuals, with a higher incidence among the elderly[3].The prevalence of vitamin D deficiency varies based on factors such as geography, season, and dietary fortification[4,5].

The role of preoperative optimization for vitamin D deficiency on outcomes of total joint arthroplasty (TJA) has been recognized recently. Studies revealed that 13 to 75% of patients undergoing total knee arthroplasty (TKA) have vitamin D deficiency [6–9]. This deficiency is associated with manipulation under anesthesia, lower functional scores [10,11], higher postoperative pain [12], extended hospital stays [11,13], and increased rates of periprosthetic joint infection (PJI) [14], and mortality in sepsis patients[15]. Zajonz et al. prospectively evaluated the impact of vitamin D on total knee and hip arthroplasty in 80 patients who had PJI, 80 patients undergoing primary arthroplasty, and 80 patients undergoing revision due to aseptic loosening. They reported no significant differences in vitamin D levels between the groups. However, they noted that vitamin D levels were statistically significantly lower in patients who had acute PJI compared to those who had chronic PJI [16]. Low vitamin D levels in patients who have PJIs have been reported in orthopaedic literature[14,17,18] . Yet, there is currently limited data on whether vitamin D deficiency in the early postoperative period following primary arthroplasty poses a risk factor for PJI and wound problems.

Despite the emphasized significance of restoring vitamin D levels to within normal parameters, standardization regarding the methods and timing of vitamin D optimization remains unclear. A study conducted by Maniar et al. analyzed 214 patients who underwent TKA, with a particular focus on 120 individuals who have preoperative vitamin D assessments. Patients were stratified into two cohorts based on their vitamin D levels (< 30 ng/mL and ≥ 30 ng/mL) and subsequently received oral vitamin D supplementation for four weeks postoperatively. Findings revealed that the supplementation regimen led to enhanced functional recovery, as determined by Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores, particularly evident among TKA patients who had preoperative vitamin D insufficiency, thereby suggesting a comparable recovery trajectory

to those who had adequate vitamin D levels. [19]. Mouli et al. compared two preoperative supplementation methods in 174 vitamin D-deficient patients undergoing TKA: daily D3 doses (1,000 to 6,000 IU) and a loading dose of 50,000 IU weekly for 4 weeks, followed by 2,000 IU/d. Results showed a more effective correction of deficiency in the loading dose group (73.3 versus 42.4% in the daily group) and a greater increase in vitamin D levels[20]. Additionally, a systematic review indicated that a single oral dose of 300,000 IU of D3 vitamin maintained serum D vitamin levels above 30 ng/mL for 12 weeks in elderly individuals who had serum D vitamin levels below 20 ng/mL. Following oral administration, serum D vitamin concentration begins to rise from day one, reaching peak levels on days three and seven [21].

In this study, we aimed to investigate the impact of vitamin D replacement on PJI in a cohort comprising more than 1,000 patients. Our hypothesis posits that the preoperative administration of a single oral dose of 300,000 IU of D3 vitamin to patients who had vitamin D deficiency would reduce postoperative complications, particularly focusing on the reduction of PJIs.

Materials and Methods

Study Design and Participants

A multicenter study involving three institutions was designed, which retrospectively reviewed the prospectively collected data of 1,400 patients, who underwent primary THA or TKA between 2019 and 2022 with a minimum follow-up of three months. There were two distinct groups that were established, each consisting of 700 patients. The study group encompassed consecutive patients who had documented serum vitamin D levels within 2 two weeks before surgery, while the control group comprised consecutive patients whose serum vitamin D levels were unknown.

Data Collection

Information regarding comorbidities was obtained through a combination of patient self-reports, anesthesia notes, and a review of electronic medical records. Patient statements provided insights into smoking and alcohol consumption habits, while laboratory data were extracted from the electronic records of participating

hospitals. The use of diverse data sources ensured a comprehensive and accurate representation of comorbid conditions and lifestyle factors. The electronic medical records of the participating hospitals served as a robust repository for accessing detailed laboratory data, enhancing the depth and reliability of the collected information. The triangulation of these sources contributes to the richness and reliability of the dataset, supporting a comprehensive evaluation of the impact of comorbidities on the study outcomes. Patients were scheduled for follow-up appointments at the second week and third month post-discharge, unless they reported no intervening health problems. Patients were instructed to report any new complaints during this period. Those experiencing new or worsening symptoms were encouraged to attend unscheduled follow-up visits for evaluation.

Exclusion Criteria

Exclusion criteria were implemented to establish a robust study cohort, excluding individuals who had follow-up durations of fewer than 90 days, those who have acute hepatitis, cancer, organ transplant recipients, individuals on dialysis, those receiving extra supplementation postoperatively within 90 days, and patients under the age of 18 years. Additionally, patients who had known preoperative serum vitamin D levels exceeding 30 ng/mL were also excluded.

Study Population

Following the exclusion criteria, the final study population comprised a total of 1,080 patients, with 488 (45,1%) patients assigned to the study group (Vitamin D replacement group: patients whose vitamin-D level is less than 30 ng/mL and who received a single dose of oral 300,000 IU vitamin D within two weeks preoperatively) and 592 patients (54,9%) assigned to the control group (whose vitamin-D level is unknown) (Figure 1). The participants had a mean age of 64 years (range, 21 to 96). Of those, 80% were women and 700 patients (64.8%) underwent TKA. Details regarding demographic data, smoking status, alcohol use, and body mass index (BMI) are presented in Table 1.

Outcomes

Our primary objective is to investigate whether vitamin D replacement reduces the rates of PJI and superficial wound problems within 90 days postoperatively. The diagnosis of PJI was determined based on the

Musculoskeletal Infection Society (MSIS) criteria[22]. Dehiscence of the incision area, superficial discharge, and infections that did not extend beneath the fascia were considered superficial wound problems. Our secondary aim is to examine whether there is a difference in readmission rates, postoperative medical complications, including acute kidney injury, pneumonia, venous thromboembolism, acute pulmonary edema, acute myocardial infarction, as well as other surgical complications, including cellulitis, dislocation, and periprosthetic fracture, between the vitamin D replacement and control groups .

Ethical Approval

Informed consents were waived, and Institutional Review Board (IRB) approval was granted under the protocol number E-10840098-772.02-2644.

Data Analyses

A power analysis was conducted using G-Power 3.1 software (Heinrich-Heine-Universität Düsseldorf, Germany) to determine the minimum sample size required for detecting a clinically significant difference in 90-day PJI rates. With a Type I error rate of 0.05 ($\alpha = 0.05$) and 95% power ($\beta = 0.80$), the estimated sample size was 651 patients per group, based on an effect size of 0.2. However, challenges in patient recruitment resulted in 488 patients for the intervention group and 592 patients for the control group. Subsequent *post hoc* analysis, based on our study data, revealed a test power of 90%. Despite deviating from the initially targeted sample size, this analysis provided valuable insights.

The data was analyzed using SPSS software (version 29.0; IBM Corp., Armonk, New York, USA). To assess the normality of the data distribution, skewness and kurtosis values were utilized as statistical measures. Categorical variables were compared using the Pearson *Chi*-square test, while an independent sample *T*-test was employed to compare parametric variables. To identify risk factors for both PJI and superficial wound problems over the course of 90 days, we first conducted univariate logistic regression analyses. Subsequently, we employed multiple logistic regression models, adjusting them for all covariates with a *P*-value less than 0.2 in the univariate analyses, as well as covariates that may be deemed clinically important. When conducting the regression analysis, patients under the age of 65 and those who have a BMI less than 30 were selected as the reference group.

Quantitative variables were presented as the mean $\pm$ standard deviation, and qualitative variables were expressed as numbers (n), frequencies, or ratios. Statistical significance was considered for *P*-values less than 0.05.

Results

The mean serum vitamin D level of the 488 patients in the vitamin D replacement group was 16.7 ng/mL $\pm$ 6.8. The control group tended to stay significantly longer in the hospital compared to the study group (3.3 ± 1.46 versus 2.3 ± 1.53 days, respectively; $P < 0.001$). An extended hospitalization was found for both TKA (3.46 versus 2.08 days, $P < 0.001$) and THA (3.12 versus 2.36 days, $P < 0.001$) patients who were deficient in vitamin D compared to the control group.

When accompanying comorbidities were examined, the vitamin D replacement group notably exhibited a higher prevalence of coronary artery disease (CAD) (15.8%) and chronic obstructive pulmonary disease (COPD) (10.5%) compared to the control group (CAD: 7.6%, COPD: 1.5%), both statistically significant ($P < 0.001$). Additionally, renal disease was significantly more prevalent in the vitamin D replacement group (2.3%) than in the control group (4.9%) ($P = 0.022$). (Table 2)

Comparing the two groups regarding postoperative complications, acute pulmonary edema was significantly lower in the vitamin D replacement group (0.3%) compared to the control group (1.4%), with a $P = 0.039$. Additionally, the vitamin D replacement group exhibited significantly lower rates of superficial wound problems (0.2 versus 2.5%, $P = 0.002$) and cellulitis (0.0 versus 2.2%, $P = 0.001$). The total number of complications was significantly reduced in the vitamin D replacement group (4.3%) compared to the control group (8.6%), with a P value of 0.005. (Table 3)

The prevalence of PJI in our cohort was found to be 1% (11 of 1,080). There was no statistically significant difference between the vitamin D replacement and control groups (0.6 versus 1.4%, respectively; $P = 0.23$). Additionally, in both univariate and multivariate analyses, no significant relationship was identified between vitamin D replacement and PJI ($P = 0.73$; OR [odds ratio]: 1.27 with 95% CI [confidence interval]: 0.32 to 5).

Acute pulmonary edema and acute myocardial infarction showed significant differences in the THA subgroup (both $P = 0.038$), with higher rates in the control group. These two parameters were not statistically

different in the TKA group ($P = 0.296$ and $P = 0.460$, respectively). In TKA patients, superficial wound problems (2.5 and 0%, respectively, $P = 0.015$) and cellulitis rates (2.8 and 0%, respectively, $P = 0.011$) were higher in the vitamin D replacement group compared to the control group. Despite a higher incidence of superficial wound problems in the control group undergoing THA, no statistically significant difference was observed between the groups (2.5 versus 0.4%, $P = 0.063$).

In the univariate analyses, vitamin D replacement demonstrated a significant association between vitamin D replacement and a reduced incidence of superficial wound with an odds ratio of 12.6 (95% CI: 1.66 to 96.19, $P = 0.014$). This significant association persisted in the multivariate analysis, with an adjusted odds ratio of 15.01 (95% CI: 1.78 to 126.3, $P = 0.013$). Sex, surgery type, bilateral surgery, age at surgery, BMI, CAD, COPD, smoking, and alcohol use did not show significant associations with superficial wound problems in both univariate and multivariate analyses. These findings suggest that vitamin D supplementation is independently associated with a reduced risk of superficial wound problems after surgery. (Table-5)

Discussion

The findings of this study indicate that a high single dose of preoperative vitamin D supplementation may reduce postoperative complications. While our study confirmed a portion of our hypothesis by validating that vitamin D replacement reduces the risk of postoperative wound problems and cellulitis, on the other hand, we were unable to substantiate our hypothesis that vitamin D replacement diminishes the risk of PJI in the early postoperative period. Moreover, the replacement of vitamin D deficiency may reduce the occurrence of wound problems in the first 90 days postoperatively. To the best of our knowledge, this study represents the first comparison between patients who have vitamin D deficiency receiving a preoperative single dose of 300,000 IU vitamin D replacement and those who have an unknown deficiency of vitamin D status undergoing primary TKA and THA.

Optimizing vitamin D levels has been demonstrated to improve postoperative scores and reduce the risk of complications in both primary and revision TJA [19,23,24]. However, the optimal dose and application route of vitamin D remain contemporary topics with limited consensus, and the number of studies on this subject is relatively scarce. In a randomized controlled trial comparing patients who received 50,000 IU of vitamin D3 supplementation on the day of surgery with those who received placebo treatment, Weintraub et al. did not find a

significant difference in functional results and complication rates[25]. Moreover, in a placebo-controlled trial by Mak et al., 218 adults aged 65 or older undergoing hip fracture surgery received either a cholecalciferol loading dose (250,000 IU vitamin D3) or a placebo, along with daily vitamin D (800 IU) and calcium (500 mg) for 26 weeks. The group receiving the loading dose exhibited elevated 25-OHD levels at weeks 2 and 4, along with a decrease in falls[26]. In a recent study with 60 patients undergoing TKA, three groups were established based on vitamin D levels and supplementation methods. Patients receiving oral high-dose supplementation exhibited a more pronounced increase compared to those receiving intramuscular supplementation. The study highlighted that oral supplementation promptly corrected vitamin D insufficiency, and functionally, this effect remained consistent over the two weeks following surgery[27]. We administered a single 300,000 IU dose of vitamin D3 to patients who have vitamin D deficiency, adhering to the protocol proposed by Kearns et al.[21], within two weeks before surgery. Compared to the control group, we noted reduced complication rates in these patients throughout the three-month postoperative period.

The biologically active form of vitamin D3, not only regulates bone and calcium metabolism but also exhibits immunomodulatory effects by interfering with nuclear transcription factors and directly interacting with vitamin D-responsive elements in cytokine gene promoters [28–30]. Recent studies indicate that patients undergoing revision surgery due to infection exhibit low serum vitamin D levels [9]. A mouse model of PJI by Hedge et al. showed that deficiency in vitamin D3 leads to heightened bacterial burden and neutrophil infiltration, and this can be reversed through preoperative repletion of vitamin D [17]. In a retrospective study involving 6,593 patients, 868 of whom had vitamin D deficiency, the cohort with inadequacy demonstrated elevated risks of surgical site infection necessitating irrigation and debridement, as well as prosthesis removal, at the one-year follow-up. Notably, no replacement therapy was administered to the patients during the preoperative period in this particular investigation [14]. On the contrary, in a study examining patients undergoing revision surgery, Signori et al. revealed, that in both aseptic and infection-related cases, serum vitamin D levels were below reference values. However, they observed that the average values of vitamin D levels in patients who have infections were significantly higher than those in aseptic patients [18]. In our cohort, we observed no significant difference in terms of acute PJI between the two groups. However, we found that the vitamin D replacement group had a lower incidence of superficial wound problems and cellulitis, especially in TKA group. We acknowledge that there are numerous factors that cause postoperative wound problems after TJA. This study suggests that the administration of vitamin D replacement may have a role in reducing the development of wound problems following TJA. The

immunomodulatory role of vitamin D, with its positive effects on macrophages and dendritic cells, could explain these outcomes. However, the higher incidence of superficial wound problems and cellulitis in TKA patients may be attributed to the thinner subcutaneous tissue, variations in tension between wound edges with flexion-extension, and the observed skin dryness in this region.

Low vitamin D levels have been demonstrated to prolong the duration of intensive care unit stays following cardiac procedures [31]. Notably, in geriatric patients' units, it independently doubles the length of stays beyond 14 days and increases it 4.8 times when combined with other risk factors such as delirium and male gender [32,33]. Furthermore, current studies show a relationship between vitamin D deficiency and prolonged hospitalization time in patients who underwent TJA [11]. In their study involving 1,083 patients undergoing total TKA and THA, Maier et al. noted an extended hospital stay in the group with vitamin D deficiency (15.6 versus 11.3 days, respectively). Moreover, their multivariate analyses revealed a significant association between vitamin D deficiency and LOS [34]. Similarly, Traven et al. noted an association between low vitamin D levels and prolonged hospitalization in patients undergoing revision arthroplasty, although statistically insignificant (5 versus 3.6 days, $P = 0.086$) [13]. Unlike these studies, a cohort of 200 THA patients stratified into three groups based on their vitamin D levels (sufficient, insufficient, and deficient) indicated similar lengths of hospital stay among the groups [35]. Moreover, the literature is lacking on postoperative medical complications in patients who have vitamin D deficiency.—Hedge et al. demonstrated that hypovitaminosis D exhibits higher rates of postoperative complications, including deep venous thrombosis, myocardial infarction, and cerebrovascular accidents [14]. Our cohort identified an increased incidence of acute myocardial infarction and acute pulmonary edema in patients undergoing THA with lower levels of serum vitamin D ($P = 0.038$), aligning with the literature, indicating that patients receiving vitamin D replacement therapy have a shorter duration of hospitalization.

This study has several potential limitations. The cohort includes consecutively operated patients within a specific time frame. Factors such as sex, type of arthroplasty, and age were not matched. Although the presence of acute myocardial infarction and acute pulmonary edema showed statistical significance, the limited number of patients who have this complication is low, which prevented us from conducting multivariate analysis. Various factors, including culture, lifestyle, regional factors, and comorbidities, may influence vitamin D levels. Additionally, the amount of sunlight exposure patients receive after surgery is unknown. Also, we provided the same dose of replacement therapy to all patients without considering the degree of deficiency. We did not measure

patients' vitamin D levels in the postoperative period, and we are unaware of the extent of vitamin D deficiency in the control group. Although this might be perceived as a limitation, the control group actually does represent the current status of patients undergoing TJA. Considering previous prevalence studies have indicated that vitamin D deficiency ranges from 60 to 95% in the adult and geriatric age groups in Turkey, our control group almost represents the entire population undergoing TJA[36,37]. Despite these limitations, the strengths of the study include its multicenter nature, inclusion of patients who have had regular follow-ups for three months, and a large sample size. Considering PJI incidence at 1% after TJA, future studies with larger cohorts may identify the relationship between vitamin D deficiency and PJI.

In conclusion, this study establishes that addressing vitamin D deficiency emerges as a modifiable risk factor for preventing postoperative wound complications. Administering an oral 300,000 U single-dose vitamin D regimen to correct vitamin D deficiency can positively impact outcomes following primary TJA. This simple replacement strategy serves as a proactive measure to preemptively address potential wound problems before they occur.

Declaration of Generative AI and AI-Assisted Technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to edit language. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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FIGURES

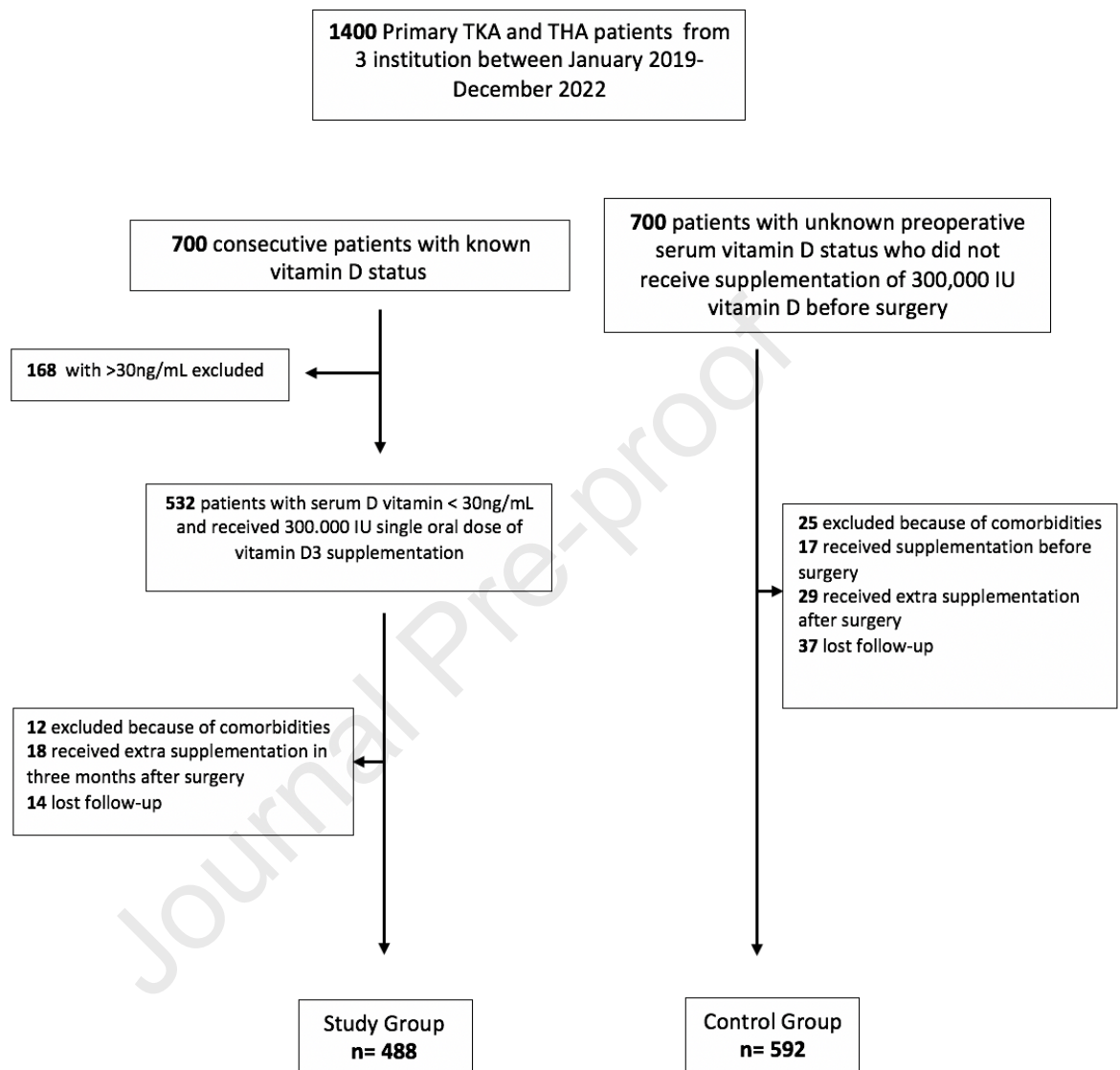


Figure-1 : Flow diagram of participants

TKA: Total Knee Arthroplasty ; THA: Total Hip Arthroplasty

Tables

Table 1 : Demographics of patients

	Vitamin D replacement Group n=488	Control Group n=592	Overall n=1080	<i>P</i> value
Age, mean ($\pm$ SD)	63.4 ($\pm$ 14.7)	66 ($\pm$ 11.1)	64.8 ($\pm$ 12.9)	0.001
Women (%)	360 (61.2)	501 (84.6)		0.001
BMI, mean ($\pm$ SD)	30,2 ($\pm$ 4)	32,2 ($\pm$ 6.1)	31,3 ($\pm$ 5,2)	0.004
Surgery type ,TKA (%)	229 (46.9)	471 (79.5)	700 (64.8)	0.001
Smoking, reference: yes (%)	65 (13.3)	32 (5.4%)	97 (9)	0.001

SD: Standard deviation, BMI: Body-mass index, TKA: Total Knee Arthroplasty

Significance is defined for the *P* value < 0.05

Table 2: Comorbidities of patients

Comorbidities	Vitamin D replacement group (n=492) (%)	Control group (n=588) (%)	<i>P</i> value
CAD	45 (7.6)	77 (15.8)	<0.001
COPD	9 (1.5)	51 (10.5)	<0.001
Asthma	42 (7.1)	35 (7.2)	0.96
Thyroid disorder	63 (10.6)	44 (9)	0.374
Diabetes mellitus	389 (65.7)	292 (59.8)	0.132
Hypertension	175 (29.6)	150 (30.7)	0.771
Renal disease**	29 (4.9)	11 (2.3)	0.022

*Chi-square test was used to compare the categorical variables between groups

CAD: Coronary artery disease ; COPD: Chronic obstructive pulmonary disease

**not required dialysis

Significance is defined for the *P* value < 0.05

Table 3: Complication rates after surgery

Variable	Vitamin D replacement group (n=492) (%)	Control group (n=588) (%)	P value
Acute kidney injury	0.2	0.2	0.683
Pneumonia	0.4	1.2	0.165
Venous thromboembolism	0.2	0.8	0.159
Acute pulmonary edema	0.3	1.4	0.039
Acute myocardial infarction	0.4	0.7	0.559
Periprosthetic fracture	1	0.8	0.759
Dislocation **	1.2	0.8	0.768
Acute periprosthetic infection	0.6	1.4	0.230
Superficial wound problems	0.2	2.5	0.002
Cellulitis	0.0	2.2	0.001
90-days readmission	3.9	4.4	0.683
Total number of complications	4.3	8.6	0.005
Mortality	0.8	0.5	0.524

*Chi-square test was used to compare the categorical variables between groups

**Only for patients who underwent total hip arthroplasty

Significance is defined for the P value < 0.05

Table 4: The post-operative complications regarding the surgical type

Variable	Total Knee Arthroplasty			Total Hip Arthroplasty		
	Control group (n=471) (%)	Vitamin D replacement group (n=229) (%)	P value	Control group (n=121) (%)	Vitamin D replacement group (n=259) (%)	P value
Acute kidney injury	0.2	0.4	0.602	none	none	
Pneumonia	1.3	0.9	0.640	0.8	none	0,143
Venous thromboembolism	0.8	0.4	0.543	0.8	none	0.143
Acute pulmonary edema	1.3	0.4	0.296	1.7	0.4	0.038
Acute myocardial infarction	0.4	0.9	0.460	1.7	0.4	0.038
Periprosthetic fracture	0.6	0.9	0.727	1.7	1.2	0,693
Dislocation	none	none		0.8	1.2	0,768
Acute periprosthetic infection	1.4	0.6	0.500	0.8	0.4	0,500
Superficial wound problems	2.5	none	0.015	2.5	0.4	0,063
Cellulitis	2.8	none	0.011	none	none	
90-days readmission	4.9	4.8	0.953	2.5	3.1	0,741
Total number of complications	10	5.7	0.056	3.3	3.1	0,910
Mortality	0.6	1.7	0.166	none	none	

*Chi-square test was used to compare the categorical variables between groups
Significance is defined for the P value < 0.05

560 **Table 5: Univariate and multivariate analysis of risk factors for superficial wound problems**

	Univariate analysis		Multivariate Analysis	
	Odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Vitamin D supplementation	12.6 (1.66-96.19)	0.014	15.01 (1.78-126.3)	0.013
Gender (Reference: Female)	0.56 (0.12-2.47)	0.442	0.43 (0.08-2.3)	0.331
Surgery Type (Reference: TKA*)	0.61 (0.12-1.92)	0.395	0.93 (0.2-4.25)	0.924
Bilateral surgery	1.12 (0.12-6.95)	0.924	0.79 (0.1-6.3)	0.828
Age at surgery reference: <65)	1.09 (0.15-7.93)	0.296	1.1 (0.09-10.1)	0.384
BMI (reference: <30)	1.78 (0.56-5.64)	0.237	0.83(0.08-8.3)	0.870
CAD	1.12 (0.25-5)	0.878		
COPD	0 (0-0)	0.997		
Renal Disease	3.1 (0.84-17.5)	0.081	2.6 (0.5-13)	0.228
Smoking	1.45 (0.32-6.5)	0.622	2.9 (0.55-15.3)	0.201
Alcohol Use	0 (0-0)	0.996		

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563 TKA: Total knee arthroplasty CAD: Coronary artery disease ; COPD: Chronic obstructive pulmonary disease ;
564 CI: Confidence interval

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566 Significance is defined for the *P* value < 0.05
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