Journal of Orthopaedics 34 (2022) 8–13

Contents lists available at ScienceDirect

Journal of Orthopaedics

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

Influence of vitamin D levels on outcomes and nosocomial COVID-19 infection in patients undergoing total knee arthroplasty- a cohort study

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ARTICLE INFO

Keywords:
Vitamin D3
Nosocomial COVID-19
Functional outcomes
Total knee arthroplasty
COVID-19

ABSTRACT

Purpose: This study aimed to audit the effects of vitamin D3 on the early functional outcomes, the incidence of nosocomial COVID-19 infection and complications in patients undergoing elective Total Knee Arthroplasty (TKA).

Methods: This was a retrospective study involving patients undergoing primary unilateral TKA between January 2020 to May 2021 operated by a single surgeon using a single implant. Participants were divided into two cohorts, Deficient-vitamin D3 level <20 ng/ml and Sufficient-vitamin D3 level ≥20 ng/ml. Assessment for Knee Society Score and Oxford Knee Score (OKS) was done preoperatively and one year after TKA. Nosocomial COVID-19 infection rate, 30-day re-admissions and complications were noted during the study.

Results: 235 patients were divided into 2 cohorts matched by age, gender and ASA grades. 74 patients belonged to the deficient group and 161 belonged to the sufficient group. The mean preoperative scores in the sufficient group were higher than the deficient group (OKS = 15.74 vs 12.95; KSS = 88.91vs 85.62). Similarly, the one-year postoperative scores in the sufficient group were significantly higher (OKS = 36.54 vs 35.16; KSS = 164.01 vs 161.22). A linear correlation was present between preoperative score (r = 0.273) & post-operative scores (r = 0.141) with serum vitamin D3 levels. Vitamin D3 deficient individuals had higher nosocomial COVID-19 infection rate (10.81% vs 4.96%,p = 0.16). The incidence of complications like DVT, embolism, stroke, infection and fracture were not statistically different in the two groups.

Conclusion: Vitamin D positively influences the outcomes of TKA and protects against nosocomial COVID-19 infection in patients undergoing elective TKA.

1. Introduction

The SARS-CoV-2 coronavirus (COVID-19) was declared an international public health emergency on the January 30, 2020.[1] A nationwide lockdown was announced by the government of India on March 24, 2020, to curb the spread of this novel virus.[2] Elective surgeries nationwide, including arthroplasty, bore a major brunt of lockdown as a majority of the healthcare resources were directed towards the management of COVID-19.[3]

Patients suffering intolerable knee pain during the COVID-19 pandemic expressed their dissent worldwide due to the restricted access to Total Knee Arthroplasty (TKA), an elective surgical procedure.[4] It was a challenge for the orthopaedic community worldwide to balance the benefit of the surgery with a higher risk of acquiring the infection.

Vitamin D, a seco-steroid produced in the skin, plays an important role in calcium and phosphate homeostasis.[5] Newer evidence has shone a light on the role of vitamin D in immune and cell signaling pathways.[6] Deficiency of vitamin D has been associated with adverse postoperative outcomes, longer hospital stays and prosthetic joint infections (PJI) in patients undergoing total joint arthroplasty.[7–9]

Various studies report a high incidence of vitamin D deficiency in patients undergoing TKA, ranging from 36.4 to 76.2%.[10] This deficiency

Abbreviations: TKA, total knee arthroplasty; KSS, Knee Society Score; OKS, Oxford Knee Score; COVID-19, Coronavirus Disease 2019; PJI, Prosthetic Joint Infections; BMI, Body Mass Index; ASA, American Society of Anaesthesiologist; LOS, Length of Hospital stay; RTPCR, Real-Time Polymerase Chain Reaction; PFC, Press Fit Condylar; BOA, British Orthopaedic Association; SD, Standard Deviation; ICU, Intensive Care Unit.

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https://doi.org/10.1016/j.jor.2022.07.022
Received 5 July 2022; Accepted 28 July 2022
Available online 2 August 2022

may be attributed to restricted mobility and outdoor activity associated with advanced osteoarthritis.[11] Restricted outdoor activity and work-from-home culture owing to COVID-19 lockdown have been reported to add to the burden of vitamin D deficiency in a country like India where it is already rampant.[12]

Owing to the controversial literature regarding the role of vitamin D3 on the results of TKA and its effect on complications, this study aimed to audit the functional results and complications of total knee arthroplasty in two cohorts of patients, those deficient and sufficient in serum vitamin D3 levels, operated by a single surgeon, in a high-volume arthroplasty centre, during the era of the novel COVID-19 pandemic. We also aimed to study the incidence of 30-day re-admissions and peri-operative nosocomial COVID infection in this group of patients.

2. Materials and methods

A retrospective observational study was undertaken at our tertiary care orthopaedic hospital, comparing the results and complication rates in two cohorts of patients operated for unilateral primary TKA between January 2020 to May 2021. The study was commenced after obtaining necessary ethical approvals from the Institutional Review Board (SIEC/2021/460).

Between January 2020 and May 2021, serum vitamin D3 levels were measured from the routine blood samples of all the patients awaiting TKA during their pre-admission visit. Measurements of serum Vitamin D3 levels were taken from the blood samples of all the patients, irrespective of their prior vitamin D supplementation status. A fully automated Maglumi 1000 analyzer (*SNIBE Co, Ltd, China*) was used for its measurement using the chemiluminescence immunoassay technique.

The data including serum vitamin D3 levels, serum albumin levels, baseline patient demographic data, comorbidity status, Body Mass Index (BMI), physical status classification grade (American Society of Anaesthesiologist- ASA grade), preoperative scores- Oxford Knee Score (OKS)[13] and Knee Society Scores (KSS),[14] and Length of Hospital Stay (LOS) were prospectively recorded for all the patients in the hospital database.

From this repository, data of 318 patients undergoing unilateral conventional primary TKA, operated on by a single surgeon in a single tertiary care arthroplasty centre, were retrieved. Of these, 33 patients who underwent surgery on the opposite side during the study duration were excluded. Patients with stroke, dementia and parkinsonism were also excluded to avoid significant outcome outliers. Patients who were diagnosed COVID-19 positive by Real-Time Polymerase Chain Reaction (RTPCR) during the time of admission were deferred from the surgery and excluded from the study.

All the patients were operated on by the surgeon through a standard medial parapatellar approach using cemented PFC Sigma Posterior Stabilized implant (*Depuy Inc., Warsaw, IN*). All the COVID-19 preventive precautions were taken including the 'Green safe pathways' as per the guidelines of the British Orthopaedic Association (BOA) which were suitably modified for the existing infrastructure to provide safe corridors for care during hospital admission.[15] All hospital personnel were trained concerning the donning/doffing procedures with a separate area earmarked near the operating room. The operation theatres were thoroughly sanitized before and after the surgical procedure. Despite all the preventive measures, the risk of nosocomial and peri-operative COVID-19 infection was explained to all the patients before the surgery.

All the patients were mobilized with identical protocols and discharged on day two or three in absence of any complications. Patients having fever or COVID-19 suspected symptoms were presumptively isolated and subjected to an RT-PCR, which if positive were shifted to an isolation ward or home care as suitable.

2.1. Study cohorts

As suggested by the clinical practice guidelines of the Endocrine Society,[16] our patients were divided into two groups according to their vitamin D3 (25-Hydroxy) levels. Those having vitamin D3 levels $\geq$20 ng/ml (50 nmol/l) were deemed to be sufficient and those with concentration <20 ng/ml were deemed to be deficient. 50 patients were lost to follow-up leaving us with two cohorts of 161 and 74 patients respectively, comparable for age, gender, comorbidities and ASA grade.

2.2. Primary outcome variables

These patients were followed up at one year postoperatively when functional outcome score (KSS) and Patient-reported outcome measures (OKS) were measured by the same research fellow who measured the preoperative scores.

2.3. Secondary outcome variables

The incidence of nosocomial COVID-19 infection in all the patients was noted. Similar to the contemporary literature, nosocomial COVID-19 infection was defined as meeting the following criteria: a) Patient being tested negative on screening with an RT-PCR test during the time of admission. b) Patient developing symptomatic COVID-19 infection during the period of hospitalization or the first 14 days following discharge.[17]

The rate of readmission due to surgical causes or other non-covid medical causes within the first 30-days was also noted in both the groups.

Major complications like prosthetic joint infection, instability and fractures, pulmonary embolism, cardiovascular event, etc., and minor complications like superficial wound gaping, urinary tract infection and deep vein thrombosis were monitored during the follow-up period.

2.4. Statistical analysis

Descriptive statistics including mean, standard deviation and proportions were used for the baseline patient data like age, gender etc. Functional scores were treated as continuous variables. The normality assumption of KSS and OKS were fulfilled with the Kolmogorov-Smirnov test, allowing parametric tests to be performed. An independent *t*-test was used to test the difference between the means of the two groups. Linear co-relation between pre and post-operative scores, vitamin D3 level, age and BMI was analyzed using the Pearson correlation coefficient (r). Multivariate linear regression was used to test the relationship between postoperative scores and vitamin D3 level, adjusted for age and ASA grade. SPSS version 25 (*SPSS Inc., Chicago, IL, USA*) was used for performing the statistical analysis.

3. Results

3.1. Baseline patient demographics and preoperative status

235 patients operated for primary conventional unilateral TKA were divided into two groups, deficient (<20 ng/ml) and sufficient (>20 ng/ml) with 74 and 161 patients respectively. The mean age of the patients enrolled in this study was 63.99 years (SD = 9.42). Both the groups were comparable in their age, comorbidities, ASA grade and BMI (Table 1).

Mean serum vitamin D3 levels in the deficient group was 14.91 ng/ml (SD = 3.83), and that in the sufficient group was 33.35 ng/ml (SD = 13.07), $p < 0.0001$. Bivariate analysis revealed no correlation between the vitamin D3 levels and age, BMI and serum albumin levels (2-tailed) (Table 2).

The preoperative scores in both the groups were statistically different despite their similarity in age, comorbidities, ASA grade and BMI. The mean of preoperative OKS scores in the sufficient group was significantly higher than the deficient group (15.74 (SD = 2.453) vs 12.95(SD = 2.086); $p < 0.0001$). Similarly, the mean preoperative KSS scores were significantly higher in the sufficient group when compared

Table 1
Comparison of baseline demographic parameters between 2 cohorts.

	VIT D3 DEFICIENT (n = 74)	VIT D3 SUFFICIENT (n = 161)	P Value	TOTAL (n = 235)
	Mean (SD)	**Mean (SD)**		**Mean (SD)**
Mean Age	61.32 (±9.743)	63.99 (±9.421)	0.051	63.15 (±9.58)
Mean BMI	28.166 (±5.131)	27.495 (±3.943)	0.321	27.706 (±4.352)
Mean VIT D3 level	14.91 (±3.83)	33.35 (±13.07)	p < 0.0001*	27.55 (±13.971)
	Number (%)	**Number (%)**	**P value (chi-square)**	**Number (%)**
Sex (F:M)	41/33	90/71		131/104
ASA grade				
1	14 (18.91)	29 (18.01)	0.8677	43 (18.29)
2	53 (71.62)	126 (78.26)	0.2682	179 (76.17)
3	7 (9.45)	6 (3.72)	0.0748	13 (5.53)
HTN	50 (67.56)	109 (67.70)	0.9837	159 (67.65)
DM	27 (36.48)	55 (34.16)	0.7289	82 (34.89)
Hypothyroidism	12 (16.21)	30 (18.63)	0.6539	42 (17.87)
Respiratory illness(Asthma/ COPD)	4 (5.40)	10 (6.21)	0.8089	14 (5.95)
Inflammatory arthritis	2 (2.70)	6 (3.72)	0.6883	8 (3.40)
Coronary Artery Disease	5 (6.75)	16 (9.93)	0.4282	21 (8.93)
Chronic Kidney Disease	3 (4.05)	4 (2.48)	0.5118	7 (2.97)

VIT D3: 25-Hydroxy Vitamin D3.
BMI: Body Mass index.
F:M: Female:Male.
ASA: American Society of Anaesthesiologist.
HTN: Hypertension.
DM: Diabetes Mellitus.
COPD: Chronic Obstructive Pulmonary Disease.

Table 2
Comparison of baseline demographic parameters between 2 cohorts.

		AGE	BMI	Sr. ALBUMIN
PRE-OP VITD3	Pearson corelation co-efficient	0.119	−0.049	−0.017
	P value	0.07	0.456	0.799

**Correlation is significant at the 0.01 level (2-tailed). n = 235.

with the deficient (88.91 (SD = 5.64) vs 85.62 (SD = 5.886); p = 0.0001).

3.2. Postoperative functional assessment and analysis

There was an improvement in the mean postoperative scores after TKA in both groups. The deficient group showed an OKS improvement from 12.95(SD = 2.08) to 35.16 (SD = 4.06) whereas the sufficient group showed an improvement from 15.74(SD = 2.45) to 36.54(SD = 1.58). TKA improved the KSS scores significantly in both groups (Table 3).

Independent *t*-test revealed statistically higher postoperative OKS (36.54 (SD = 1.58) vs 35.16(SD = 4.06); p < 0.0002) and KSS scores (164.01(SD = 8.71) vs 161.22 (SD = 11.89); p = 0.044) in the vitamin D3 sufficient group when compared to the deficient group.

There was a positive linear correlation between the pre-operative and post-operative scores with vitamin D3 status. Pearson's co-efficients for preoperative and postoperative OKS were r = 0.273 (p = 0.0001) and r = 0.141 (p = 0.031) respectively. Similarly, the co-efficients for preoperative and postoperative KSS were r = 0.185 (p = 0.004) and r = 0.307 (p = 0.0001) respectively (Table 4).

Multivariate linear regression revealed a correlation coefficient of post-operative scores (KSS: r = 0.365,p = 0.0001; OKS: r = 0.191,p = 0.01) with vitamin D3 level adjusted for age and ASA grade (Table 5).

3.3. COVID-19 and other complications

8 patients (10.81%) in the deficient group and 8 patients (4.96%) from the sufficient group suffered from symptomatic nosocomial COVID-19 infection. Three of the eight from the deficient group required readmission for the same. None of the patients required ICU stay. The median duration from discharge to the onset of symptoms was 5.6 days, fitting into the definition of nosocomial infection where symptoms related to COVID-19 infection started during or within 14 days of discharge. Though the difference in COVID-19 incidence among the two groups was statistically insignificant (p = 0.16), it was clinically significant.

Complication rates among both the groups were analyzed (Table 6), however, the power of the study was inadequate to prove its statistical relevance. Analysing the 30-day re-admission rates between the two groups, the deficient group had three COVID-19 related re-admission requiring supplemental oxygen and steroids and one patient was admitted for disorientation due to hyponatremia. Among the sufficient group, two patient were admitted for Non-COVID medical reasons (acute diarrhoea and hyponatremia).

Among the other complications, there were no significant differences in the rate of Deep vein thrombosis (p = 1), Pulmonary thromboembolism (p = 0.3149), perioperative fracture (p = 0.5316), deep infection (p = 0.5316), Cerebrovascular event (p = 0.3149), Urinary tract infection (p = 1).

Table 3
Preoperative and Post-operative scores in vitamin D3 deficient and sufficient groups.

	OKS		KSS		**P value** (Independent *t*-test)
	Pre-op Mean (SD)	**Post Op Mean (SD)**	**Pre-op Mean (SD)**	**Post Op Mean (SD)**	
Vitamin D3 Deficient (n = 74)	12.95 (2.086)	35.16 (4.065)	85.62 (5.886)	161.22 (11.891)	P < 0.00001
	Pre-op Mean (SD)	**Post Op Mean (SD)**	**Pre-op Mean (SD)**	**Post Op Mean (SD)**	**P value**
Vitamin D3 Sufficient (n = 161)	15.74 (2.453)	36.54 (1.581)	88.91 (5.646)	164.01 (8.717)	P < 0.00001
P value (Independent *t*-test)	P < 0.0001	P < 0.0002	P = 0.0001	P = 0.044	

OKS: Oxford Knee Score.
KSS: Knee Society Score.
SD: Standard deviation.

Table 4
Bivariate analysis of pre and post-operative scores with different variables.

		PREOP KSS	PREOP OKS	POST OP KSS	POST OP OKS	VIT D3	Age	BMI	SerumAlbumin
PREOP KSS	r	1	0.672**	0.063	0.172**	0.185**	−0.015	−0.102	0.089
	Significance		0.0001	0.338	0.008	0.004	0.825	0.119	0.173
PREOP OKS	r	0.672**	1	0.05	0.164**	0.273**	0.07	−0.126	0.057
	Significance	0.0001	–	0.446	0.012	0.0001	0.283	0.054	0.387
POST OP KSS	r	0.063	0.05	1	0.571**	0.307**	−0.294	−0.029	−0.053
	Significance	0.338	0.446	–	0.0001	0.0001	0.0001	0.653	0.416
POST OP OKS	r	0.172**	0.164*	0.571	1	0.141**	−0.255	−0.125	−0.02
	Significance	0.008	0.012	0.0001	–	0.031	0.0001	0.056	0.764
VITD3	r	0.185**	0.273**	0.307**	0.141**	1	0.119	−0.049	−0.017
	S Significance	0.004	0.0001	0.0001	0.031	–	0.07	0.456	0.799

* Significant co-relation at $p < 0.05$.
** Significant co-relation at $p < 0.001$.
VIT D3: 25-Hydroxy Vitamin D3.
PREOP KSS: Preoperative Knee Society Score.
PREOP OKS: Preoperative Oxford Knee Score.
POST OP KSS: Post-Operative Knee Society Score.
POST OP OKS: Post-Operative Oxford Knee Score.

Table 5
Multivariate linear regression for co-relation of OKS & KSS with preoperative vitamin D3 adjusted for age and ASA grade.

Factors influencing post op KSS by multivariate regression (ASA, Vitamin D3, Age)				**Adjusted r2 = 0.308**		
Variable	Unstandardized co-efficient	Std. error	Standardised co-efficients	P value	Lower-bound at 95%	Upper bound at 95%
VIT D3	0.258	0.039	**0.365**	0.0001	0.182	0.335
Age	−0.303	0.057	−0.293	0.0001	−0.415	−0.191
ASA grade	−7.092	1.15	−0.339	0.0001	−9.358	−4.827
Factors influencing post op OKS by multivariate regression (ASA, Vitamin D3, Age)				**Adjusted r2 = 0.189**		
Variable	Unstandardized co-efficient	Std. error	Standardised co-efficients	P value	Lower-bound at 95%	Upper bound at 95%
VIT D3	0.037	0.011	**0.191**	0.01	0.014	0.06
Age	−0.066	0.017	−0.235	0.0001	−0.099	−0.033
ASA grade	−1.872	0.34	−0.328	0.0001	−2.541	−1.203

VIT D3: 25-Hydroxy Vitamin D3; ASA: American Society of Anaesthesiologist.

Table 6
Complications among the two cohorts.

	Vitamin D3 Deficient (n = 74)	Vitamin D3 sufficient (n = 161)	P*
COVID 19 Nosocomial infection	8 (10.81%)	8 (4.96%)	0.16
30 day re-admissions	3- COVID-19 1- Hyponatremia	1- Acute diarrhoea 1- Hyponatremia	0.0802
DVT	0	1 (0.621%)	1
Perioperative Fracture	1 (1.35%)	1 (0.621%)	0.5316
Deep Infection	1 (1.35%)	1 (0.621%)	0.5316
PTE	1 (1.35%)	0	0.3149
Stroke	1 (1.35%)	0	0.3149
UTI	1 (1.35%)	2 (1.24%)	1

*: Fischer's exact test for 2X2 contingency at 0.05 significance level.
DVT: Deep vein thrombosis; PTE: Pulmonary thromboembolism; UTI: Urinary tract infection.

4. Discussion

The novel COVID-19 virus has caused a high toll on life and the economy worldwide infecting millions of people worldwide.[18] The surge of COVID-19 began in March 2020 and experienced a classical wave pattern similar to any other pandemic.[19] Considering the non-availability of any specific treatment for this fast-spreading and potentially lethal illness, the lockdown was the only feasible strategy for damage control. The nationwide lockdown in India was divided into 4 phases where complete restriction of public movement was imposed.[20] Gradual relaxations were subsequently introduced after a plateau in the number of cases. Amidst this phase of relaxation, the arthroplasty services were gradually re-introduced with precautionary 'green recovery pathways' in place.

Literature supports higher perioperative mortality, post-operative complications and intensive care unit (ICU) admissions in confirmed perioperative COVID-19 infections.

Mortality as high as 30.5% was seen in patients undergoing emergency surgery for hip fractures with concomitant COVID-19 infection.[21] Higher mortality could have been attributed to a higher pro-inflammatory body status arising out of a synergetic effect of trauma, surgery and concomitant COVID-19 infection.[22] Similar complications have been described for cases in general surgery, gastro-esophageal, hepatobiliary, and colorectal surgery with concomitant COVID-19 infection.[23]

Literature supports relatively benign postoperative course in patients undergoing elective orthopaedic surgeries with preventive protocols. In a study by Zorzi et al., none of 614 patients undergoing elective orthopaedic surgeries have any major complications or ICU admissions. The incidence of perioperative fever was 3%, but none of them required care other than isolation.[24]

The rate of nosocomial COVID-19 infection ranged from 4.9% to 20%, depending upon the time of the study, utilization of preventive precautions and immunization status of the study population.[25,26] Lakhani et al. found a nosocomial infection rate of 6.48% for COVID-19, which was subsequently reduced after introducing preventive protocols.[27] In our study, 16 out of 235 (6.8%) patients were diagnosed with COVID-19 infection during the first 30 days of surgery, out of which only 3 required hospital admission and none required ICU care.

In our study, there was a clinically significant (statistically insignificant) association between COVID-19 nosocomial infection and preoperative vitamin D3 status where 8 out of 74 patients from the deficient group and 8 out of 161 patients in the sufficient group were diagnosed

positive within the first 30 days. A retrospective swiss study showed significantly low levels of vitamin D3 in COVID-19 positive patients.[28] A 1.77 times greater relative risk of testing positive for COVID-19 was found in Vitamin D3 deficient patients when compared with the sufficient group in a retrospective cohort study of 489 patients.[29] Weir et al. and Demir et al. associated vitamin D deficiency with higher severity of COVID-19 owing to its role in T regulatory lymphocyte function. Lower levels of D-dimer and thus a lesser risk of intravascular coagulopathy were seen in the vitamin D sufficient group in a study by Demir et al.[30]

There are contradictory pieces of evidence for and against the co-relation of preoperative functional status and vitamin D3 levels. The majority of the studies did not associate the preoperative function with the vitamin D3 levels.[7,8] This was in contrast to our study, where the patients with lower vitamin D3 status had a poor preoperative function. It may be vise-versa, where patients with poor function and mobility have lower vitamin D3 levels due to restricted outdoor mobility and sun exposure. This view was supported by Maniar et al. who reported worse preoperative WOMAC scores in vitamin D3 deficient patients.[31]

There has been no unison among the studies co-relating post-operative clinical results with vitamin D3 status. Some studies showed comparable,[32] whereas others showed significantly worse outcomes associated with lower vitamin D levels.[8] The possible reason for the positive correlation between postoperative function and vitamin d3 levels was its possible effect on the function of the muscular system and prosthesis integration.[10]

Our study is probably the second study that has reported poor postoperative outcomes associated with vitamin D deficiency through multivariate linear regression analysis corrected for age and ASA grade. In our study, vitamin D3 levels were retrieved from the database retrospectively at the end of the study. Neither the surgeon nor the researcher was aware of the vitamin D3 status of the patient during the study duration. All the patients received a fixed drug combination of Elemental calcium (225 mg) and vitamin D3 400IU per day irrespective of their vitamin D3 status for a period of 3 months.

The limitation of our study was a small sample size, relatively short follow-up period, and unanticipation of the change in vitamin D status after surgery. Despite restriction in the usage of bolus vitamin D supplementation, several factors including a daily supplemental dosage of 400IU, improved mobility, and outdoor exposure could influence the vitamin D3 status over the period of one year. Besides, as the study included only patients undergoing unilateral TKA during the study duration, The Knee Society Score of the unoperated but affected contralateral knee, hip or spine could influence the results of the operated knee.

Though a majority of data in the study was collected prospectively, the retrospective analysis did not allow sample size calculation. However, post hoc analysis performed to test the difference between the post-operative KSS scores of the two groups with an alpha value of 0.05, revealed the power (1-b error) of 0.439.

Studying a cohort of patients operated by a single surgeon, using a single implant during the tough COVID-19 era was the strength of this study. A study by Maniar et al. has shown the benefit of preoperative bolus oral vitamin D3 supplementation over the functional outcomes of TKA patients.[33] This strategy could be cost-effective in improving outcomes and reducing complications in pre-diagnosed vitamin D3 deficient patients planned for an elective TKA.

5. Conclusions

Vitamin D sufficiency results in better pre-operative function and postoperative functional outcomes after TKA, and also is associated with a lesser incidence of nosocomial COVID-19 infections. Hence active screening of serum vitamin D3 status prior to an elective TKA is recommended.

Units

Vitamin D3: 1 ng/ml = 2.5 nmol/l.

Funding/sponsorship

This research did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors.

Informed consent

Informed consent was obtained from all the participants for this study.

Institutional ethical committee approval

The project was performed in accordance with the ethical principles mentioned in the Declaration of Helsinki. Ethical committee approval number for the study was: SIEC/2021/460.

CRediT authorship contribution statement

Keyur B. Desai: Methodology, Data curation, Writing – original draft. **Kishore Karumuri:** Writing – review & editing. **Shruti A. Mondkar:** Formal analysis. **Chiranjeevi Thayi:** Supervision. **Adarsh Annapareddy:** Visualization. **A.V. Gurava Reddy:** Conceptualization.

Declaration of competing interest

The authors have no competing conflict of interest.

Acknowledgments

None.

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