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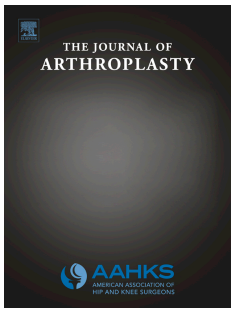

The association of calcium and vitamin D use with implant survival of total knee arthroplasty: a nationwide population based cohort study

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Abstract

Background

Calcium and vitamin D have been regarded as beneficial nutrients for bone metabolism that may affect survival of arthroplasties. However, the relationship between their use and revision rate of knee arthroplasty has not been evaluated. Thus, we investigated an association between calcium and vitamin D use and the revision rate after primary total knee arthroplasty.

Methods

A nationwide population-based cohort study was conducted using the Korean National Health Insurance database. We included patients diagnosed with knee osteoarthritis and underwent primary total knee arthroplasty between 2009 and 2018. Risk for arthroplasty revision was estimated using a Cox proportional hazards model with time-dependent covariates. Log-rank test was used to assess survival of knee arthroplasty.

Results

Out of 142,147 subjects, 28,403 were calcium and vitamin D users and 113,744 were never users. Calcium and vitamin D significantly reduced the revision risk with a 6-month drug use lag period (adjusted hazard ratio [aHR] 0.56, 95% confidence interval [CI] 0.45–0.70). Calcium and vitamin D combination use for more than 1 year was associated with reduced revision risks in both patients with periprosthetic joint infection (aHR 0.63, 95% CI 0.42–0.95) and patients without infection (aHR 0.70, 95% CI 0.54–0.91). Implant survival was significantly improved in calcium and vitamin D combination users for more than 1 year

compared with never users (log-rank $p<0.001$).

Conclusion

Combination use of calcium and vitamin D with a dose of 800 IU or greater for more than 1 year was associated with the greatest reduction in the risks for revision surgery after total knee arthroplasty.

Keywords: calcium, vitamin D, total knee arthroplasty, revision, implant survival

Introduction

Knee replacement surgery has been performed for more than 40 years and is now generally regarded as a useful and cost-effective treatment for end-stage knee arthritis[1]. It has been adopted as a main treatment modality for end-stage knee arthritis, as it improves patients' quality of life by reducing pain and enhancing long-term function[2]. In South Korea, more than 70,000 knee replacements are now performed each year and many worldwide joint registries report a similar pattern of increasing frequency[3-5].

Unfortunately, knee replacements fail for a variety of reasons, including implant loosening, infection, persistent pain, and instability, which may require revision within the lifetime of the recipient[2]. According to the 16th annual report of the National Joint Registry for England and Wales in 2019, overall revision rates at 5, 10, and 15 years were known to be 2.66%, 4.37%, and 6.41%, respectively[4]. Considering that more people will undergo revision surgery in the future due to increasing life expectancy, more efforts should be made to identify patients who are at risk of revision and to improve survival of arthroplasty.

As the implant survival is related to the quality of the surrounding bone environment[6,7], there have been several attempts to improve survival of arthroplasty with medication related to bone metabolism[8,9]. However, little is known about bone metabolism in relation to implant survival after arthroplasty. Calcium and vitamin D are representative nutrients for bone metabolism, and they have been recommended as supplements for preventing osteoporotic fractures due to their property of improving bone strength. Furthermore, vitamin D may have a potential to prevent periprosthetic joint infection after arthroplasty owing to its favourable effects on infection prevention[10]. Nevertheless, the association between calcium and vitamin D use and revision rates of knee arthroplasty has not been adequately evaluated.

Therefore, we conducted a large, nationwide population-based cohort study to investigate

whether there is any association between calcium and vitamin D use and the revision rates of primary total knee arthroplasty.

Material and Methods

Data Source

The data used in this study were extracted from the Korean Health Insurance Review and Assessment Service (HIRA) database from 2009 to 2018. The claims data of the HIRA database contain 46 million patients per year, which accounts for 90% of the total Korean population, and include claims from almost 80,000 healthcare service providers across South Korea as of 2011. It also includes sociodemographic data of the beneficiaries, patients' diagnosis based on the 10th revision of the International Classification of Disease (ICD-10), treatments, procedures, surgical history, and prescription drugs based on health insurance claims payment codes that were assigned by the Korean Centre for Disease Classification and Information[11]. This study was approved by the independent institutional review board of Severance Hospital (4–2019–0269) and was waived of the requirement of informed consent. This study adhered to the tenets of the Declaration of Helsinki.

Study Population

A nationwide population-based study was conducted using the data of subjects who had total knee arthroplasty between 2009 and 2018 (n=508,612) from the HIRA database. Patients who underwent primary total knee arthroplasty were identified by the healthcare common procedural (HCP) codes of HIRA (**Supplemental Table 1**). We excluded patients under the age of 50 years, patients without a diagnosis of knee osteoarthritis (ICD-10: M17.0, and M17.1) within a year from the day on which the primary surgery was done, patients with

history of femoral fracture (ICD-10: S72) or rheumatoid arthritis (ICD-10: M05, and M06), patients with previous claims for revision knee arthroplasty out of period, patients with two or more claimed forms of primary total knee arthroplasty during the follow-up period, patients diagnosed with osteoporosis (ICD-10: M80, M81, and M82) and prescribed bisphosphonates or selective estrogen receptor modulators, and patients who had calcium or vitamin D single agent use (**Supplemental Table 2**). Patients with two or more claimed forms of primary total knee arthroplasty were excluded as these patients may have received primary total knee arthroplasty at both legs. As the procedural code dose not inform us about the side of leg for primary total knee arthroplasty, it would be impossible to estimate the exact time interval between initial revision and its primary total knee arthroplasty at the same side of the leg in patients with primary total knee arthroplasties at both legs. Using these criteria, 366,465 (72.1%) patients were excluded, and we finally selected 142,147 participants (27.9%) (**Figure 1**).

All patients meeting the study inclusion criteria were monitored from cohort entry until the revision surgery, death from any cause, end of coverage in the database, or end of the study period (December 31, 2018, or the most recent date of data availability), whichever occurred first.

Identification of calcium and vitamin D combination users

We identified calcium and vitamin D combination users as patients who had been prescribed calcium and vitamin D combination before revision surgery with HCP codes (**Supplemental Table 2**). Never users were defined as individuals who were never prescribed the drugs or who had their first prescription of the drugs after a revision surgery. Additionally, we calculated cumulative duration of exposure to calcium and vitamin D combination by

considering the sum of all the days for which the drugs were prescribed, and the mean daily dose of use was calculated by dividing the total dose taken by the total number of days for which the drugs were prescribed. Mean daily dose was defined as the average dose rate according to the United States Federal Register[12].

Outcomes of interest

The outcomes of this study were the incidence of revision surgery in patients who had primary total knee arthroplasty and the implant survival, which was calculated as the time from primary surgery to revision surgery. We identified patients who had surgical revision with HCP codes (**Supplemental Table 1**).

Covariates and confounders

Age at primary surgery, sex, and type of insurance were included as covariates. Hospital regions were classified as metropolitan or non-metropolitan. The Charlson comorbidity index (CCI) at a year prior to primary surgery was determined by evaluating comorbid conditions[13]. Comorbidities that are known to affect arthroplasty revision rate—coagulopathy, chronic obstructive pulmonary disease, depression, diabetes, chronic kidney failure, neoplasms, and surgery related to hypocalcaemia (gastrectomy, thyroidectomy, and parathyroidectomy)—were included as time-dependent covariates[14]. As vitamin D deficiency (ICD-10: E55) was suggested as a modifiable risk factor that affects arthroplasty revision rate[15], we considered it as a time-dependent covariate as well. Osteoporosis was also considered as a time-dependent covariate because it could increase the risk of revision by lowering bone mass. Corticosteroid use was considered as a confounding factor as corticosteroids may induce osteoporosis. Other drugs that could also modify fracture risk—

proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, antiparkinsonism drugs, statins, thiazide diuretics, and anxiolytics—were included as time-dependent covariates that had the possibility of affecting the arthroplasty revision rate[8].

Statistical analyses

We first compared baseline characteristics based on calcium and vitamin D combination use using χ^2 tests for categorical variables and *t*-tests for continuous variables. We performed analyses using a Cox proportional hazards model with time-dependent covariates to examine whether calcium and vitamin D combination use was associated with the revision risk of total knee arthroplasty. The models were adjusted for age, sex, type of insurance, hospital region at primary surgery, CCI, comorbidities known to affect the risk of revision, osteoporosis, vitamin D deficiency, and use of corticosteroids and other drugs known to possibly affect fracture risk. Exposure to calcium and vitamin D was lagged by 6 months to account for the latency time and to minimize reverse causality. The risks across various cumulative durations of use and daily doses were analysed. Additionally, the risks for revision were separately assessed according to the presence of periprosthetic joint infection (ICD-10: T84.5) during the follow-up period. We used the log-rank test with Kaplan-Meier survival analyses to assess the effect of calcium and vitamin D use on implant survival. A p value <0.05 was considered significant. Statistical analyses were performed using SAS Enterprise Guide statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Out of 508,612 eligible patients with primary total knee arthroplasty, we included and followed up the data of 142,147 participants: these included 28,403 users of calcium and

vitamin D combination and 113,744 never users. The baseline characteristics of the study subjects are presented in **Table 1**. The mean ages of all study subjects, calcium and vitamin D combination users, and never users were 68.8, 68.7, and 68.9 years, respectively. Compared with calcium and vitamin D combination never users, there was female preponderance among users. More users than never users had their surgeries done in cities and metropolitan areas. Subjects who had higher CCI scores and comorbidities were more prevalent among users. Similarly, subjects who had surgeries related to hypocalcaemia, osteoporosis, and vitamin D deficiency were more prevalent among users. Use of fracture risk-associated drugs was more prevalent among users. The incidence of periprosthetic joint infection showed no difference between calcium and vitamin D combination users and never users.

During the follow-up period, 1,878 participants had revision surgery. Overall, 346 revisions occurred in calcium and vitamin D combination use group and 1,532 revisions occurred in no use group (**Table 2**). The unadjusted risks for revision are shown in **Supplemental Table 3**. After adjustment for confounding factors, the risk for revision was lower in the use group than the no use group (aHR 0.73, 95% CI 0.61–0.87; $p<0.001$). Even with a 6-month exposure lag, the aHR for revision surgery was still significant (aHR 0.56, 95% CI 0.45–0.70; $p<0.001$).

To investigate the trends in risks according to the duration of use, risks were assessed for various exposure durations since the first drug prescription (**Supplemental Table 4**). Reduced risk was observed in the subgroups who used calcium and vitamin D combination for 12 months or longer, and the risk for revision showed a gradually decreasing trend as cumulative duration of use increased.

The association between calcium and vitamin D combination use and risk of revision according to the presence of periprosthetic joint infection is presented in **Table 3**. Regardless

of infection, revision risk was reduced in subjects with calcium and vitamin D combination use for 12 months or longer. In subjects with infection, calcium and vitamin D combination use for 12 months or longer reduced the risk of revision surgery (aHR 0.63, 95% CI 0.42–0.95; p=0.03). Similarly, subjects without infection also showed a reduction in the risk (aHR 0.70, 95% CI 0.54–0.91; p=0.008).

The risk of revision according to the daily dose of calcium and vitamin D was additionally analysed (**Supplemental Table 5**). Among users with daily dose of calcium less than 1,000 mg for 12 months or longer, higher dose of vitamin D use (800 IU or more) was associated with more reduced risk (aHR 0.49, CI 95% 0.33-0.73; $p<0.001$) than lower dose (less than 800 IU) (aHR 0.75, CI 95% 0.58-0.98; $p=0.03$). Use of vitamin D dose of 800 IU or more was associated with much lowered aHR than use of vitamin D dose of 400 IU or more (aHR 0.49 for 800 IU or more and 0.69 for 400 IU or more).

In Kaplan-Meier survival analyses, among calcium and vitamin D combination users with a cumulative duration of use of 12 months or longer, a protective effect on implant survival was consistently observed throughout the follow-up periods in all subjects, both in patients with and without infection, as compared with never users (all log-rank $p<0.001$; **Figure 2A-2C**). The five-year survival probability after total knee arthroplasty increased from 98.42% to 99.48% in all subjects, from 75.25% to 93.30% in subjects with infection, and from 99.20% to 99.67% in subjects without infection, which showed the significant reduction of implant failure rate by 67.1%, 72.9%, and 58.8%, respectively (**Supplemental Table 6**). When the risk was further analysed according to the daily dose of vitamin D, implant survival was improved independent of vitamin D dose in subjects who used calcium and vitamin D combination for more than 12 months compared with never users (all log-rank $p<0.001$;**Figure 3**).

Discussion

Calcium and vitamin D are known important nutrients that are associated with bone health, but little is known about their effects on survival of knee arthroplasty. We analysed a nationwide longitudinal dataset obtained from the HIRA database, including 142,147 participants who underwent primary total knee arthroplasty with follow-up from 2009 to 2018. Our results show that patients who took calcium and vitamin D combination had significantly improved survival of their total knee arthroplasty.

We also analysed the data according to various clinically recommended doses of calcium and vitamin D combination. Even though it is still controversial whether calcium and vitamin D have protective effects on fractures[16], they have been widely used to prevent fracture caused by osteoporosis in clinical practice. In 2013, the US Preventive Services Task Force (USPSTF) recommended against daily supplementation of vitamin D at a dose of 400 IU or less and calcium at a dose of 1,000 mg or less for the primary prevention of fractures in non-institutionalized postmenopausal women (D recommendation)[17]. Recently, 1,200 mg of calcium and 800 IU of vitamin D have been recommended for the prevention of osteoporosis-induced fractures[18]. Based on these guidelines, we further investigated outcomes using subgroup analyses according to daily dose. We analysed only patients who used both calcium and vitamin D by excluding patients who used only one of the two. This drug use definition was applied to simplify cumulative duration-based subgroup analyses.

The clinical survival of arthroplasties is related to the quality of the surrounding bone environment[6,7]. Several studies have described a significant decrease in postoperative bone mineral density of up to 44% in areas adjacent to implants after total knee arthroplasty[19-22]. Periprosthetic osteolysis predates aseptic loosening, which is the most common reason for arthroplasty revision, and creates conditions that facilitate implant loosening via weakening

of the bone–implant interface. This is due to the local predominance of bone resorption over formation in periprosthetic bone[23]. Calcium supplements have been known to suppress bone turnover by about 20% and have beneficial effects on bone density by promoting bone formation[24]. Vitamin D also optimizes intestinal calcium and phosphorus absorption for proper formation of bone mineral matrix[10]. In this study, we found that calcium and vitamin D combination use decreased the aHR for risk of arthroplasty revision in subjects without periprosthetic infection and improved survival of implants. This implies that calcium and vitamin D may have an infection-independent benefit, and the increase in bone strength followed by slowed aseptic loosening and periprosthetic osteolysis could be the possible mechanism.

A classic well-known action of vitamin D is promotion of calcium homeostasis and bone health. At the same time, vitamin D has received attention for its crucial role in diverse physiological functions, and vitamin D deficiency is associated with multiple acute and chronic illnesses, including autoimmune diseases, cancers, type 2 diabetes mellitus, cardiovascular diseases, and infectious diseases [10]. With respect to immunity, vitamin D regulates innate and adaptive immune function by modulating macrophages, dendritic cells, and lymphocytes[25]. Several studies reported vitamin D deficiency is associated with increased risk of revision arthroplasty caused by periprosthetic joint infection[15,26-28]. Traven and colleagues[15] reported that low vitamin D was associated with increased risk of 90-day complication and periprosthetic joint infection as indications for revision arthroplasty. Similarly, a high frequency of vitamin D deficiency was noted in patients who underwent revision knee arthroplasty for periprosthetic joint infection[26]. These previous results suggest a potential benefit of vitamin D treatment on implant survival after total knee arthroplasty. In the current study, we also observed that calcium and vitamin D combination

use significantly decreased the aHR for revision risk in subjects with periprosthetic infection. Our results are consistent with previous reports that vitamin D use is associated with reduced risk of arthroplasty revision that is related to periprosthetic joint infection.

In the aspect of infection prevention, not only vitamin D but also calcium supplement could contribute to the reduced revision rate in the present study. There are previous studies that focused on the inhibitory effect of calcium on staphylococcal biofilm formation. Ca^{2+} participates in the signalling pathway of infection[29] and inhibits *Staphylococcus aureus* biofilm formation[30,31]. The reduction of revision rate in calcium and vitamin D users may partially attribute to the increased calcium intake in the same way.

The clinical relevance of the present study is based on several strengths. First, few studies have evaluated the clinical effects of calcium and vitamin D on survival of knee arthroplasty. To the best of our knowledge, this is the only large-scale population-based study that has been conducted on this subject till date. Second, we used a cohort from a generalized population database comprising individuals with variations in age, comorbidity, and medication. Statistical analyses with adjustments for various confounding factors diminished the risk of bias. Third, revision risks according to periprosthetic joint infection were assessed to investigate any influence of infection on the association between calcium and vitamin D use and survival of arthroplasty. Moreover, the risks of revision across various cumulative durations of use and daily doses of calcium and vitamin D were analysed to find any trend with respect to duration and amount of use, which gave more detailed information on the effect of calcium and vitamin D use.

The current study has some limitations. First, we could not take into consideration calcium and vitamin D intake from foods or over-the-counter drugs. Second, confounding due to imbalance in gender distribution between calcium and vitamin D users and non-users may

still remain, even though statistical adjustment was performed. Further studies with gender matched data needs to be conducted. Third, data about residual confounders such as bone mineral density, implant design, fixation type, and proficiency of surgeons could not be collected. Fourth, potential difference in health compliance or quality of medical management between calcium and vitamin D users and non-users may lead to bias. Since vitamin D deficiency is common, the calcium and vitamin D users may be a selected group who are more adherent to medical testing and medication with a continuity more than 1 year than non-users. Fifth, the quality of routinely collected national registry data is limited owing to input and coding errors, incomplete data, and medication non-compliance. Sixth, lifestyle-associated and anthropometric parameters such as smoking, alcohol consumption, and body mass index (BMI) were not included in the current study. Concerning smoking and alcohol consumption, no association was previously observed with revision risk on account of aseptic loosening in total knee arthroplasty[32]. Even though smoking was identified as a risk factor for periprosthetic joint infection[33,34], the surrogate comorbidity, chronic pulmonary disease, was included as the related confounder instead[35]. The association of alcohol with periprosthetic joint infection has remained controversial[36,37]. With respect to BMI, there are studies that showed the tendency of increasing risk of revision in populations with high BMI[32,35,38]. However, considering that the subjects who underwent primary total knee arthroplasty in South Korea had a relatively lower average BMI (of 25.9 kg/m^2) than Western patients[39], the influence of BMI on implant survival in the current study may have been diminished. Finally, the follow-up duration in the current study was relatively short compared with the generally expected survival of implants[40]. Therefore, it was not possible to assess long-term outcomes. Nevertheless, even over this limited follow-up period, an inverse relation was noted between calcium and vitamin D combination use and implant survival

after total knee arthroplasty.

Conclusions

Our findings demonstrated that calcium and vitamin D combination use reduces the revision risk of total knee arthroplasty both with and without infection. Combination use of calcium and vitamin D with a dose of 800 IU or greater for more than 1 year was associated with the greatest reduction in the risks for revision surgery. Considering overall high prevalence of osteoporosis and vitamin D deficiency in patients who undergo total knee arthroplasty[41-43], and potential beneficial effects of calcium and vitamin D on bone and bone-surrounding environment[10], we could suggest calcium and vitamin D supplementation for patients who undergo primary total knee arthroplasty and future clinical trials.

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Authors' Contribution Statement

Conceptualization: Y.K., and K.K.P.; Methodology, Y.K., M.H., and M.L.; Validation, Y.K., M.H., M.L., and E.H.K.; Formal Analysis, Y.K., M.H., E.H.K., and I.J.; Investigation, Y.K., M.H., and M.L.; Data Curation, Y.K., and M.H.; Writing – Original Draft Preparation, Y.K., and M.L.; Writing – Review & Editing, I.H.Y., W.S.L., H-M.K., I.J., and K.K.P.; Visualization, Y.K., and M.H.; Supervision, I.J., and K.K.P.

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None

Conflicts of Interests

The authors declare no conflict of interest that pertains to this work.

Data sharing

The data used in this study can be accessed on the homepage of the Health Insurance Review and Assessment Data Sharing Service (https://opendata.hira.or.kr/). Although the data are coded in English and numbers, and not in Korean (Hangul), the use of individual data is allowed only for Korean researchers at the moment. However, it will be possible for researchers outside the country to gain access to the data by conducting joint studies with Korean researchers.

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Table 1. Characteristics of patients in the cohort in relation to calcium and vitamin D combination use during the follow-up period

	Total (n=142,147)	Calcium and vitamin D users (n=28,403)	Never users (n=113,744)	*p* value
Age at the time of primary surgery(years)*	68.8 (7.1)	68.7 (6.7)	68.9 (7.2)	0.01
50-59	14,393 (10.1)	2,474 (8.7)	11,919 (10.5)	
60-69	60,066 (42.3)	12,649 (44.5)	47,417 (41.7)	
70-79	59,159 (41.6)	11,923 (42.0)	47,236 (41.5)	
≥80	8,529 (6.0)	1,357 (4.8)	7,172 (6.3)	
Sex (Male)	33,049 (23.2)	2,433 (8.6)	30,616 (26.9)	<0.001
Type of insurance*				<0.001
Medical insurance	133,418 (93.9)	26,206 (92.3)	107,212 (94.3)	
Medical care	8,729 (6.1)	2,197 (7.7)	6,532 (5.7)	
Hospital region of primary surgery*				<0.001
Metropolitan	42,544 (29.9)	8,951 (31.5)	33,593 (29.5)	
Non-metropolitan	99,603 (70.1)	19,452 (68.5)	80,151 (70.5)	
Charlson Comorbidity Index Score*	2.1 (1.7)	2.2 (1.7)	2.1 (1.7)	<0.001
Coagulopathy†				<0.001
No	135,898 (95.6)	26,746 (94.2)	109,152 (96.0)	
Yes	6,249 (4.4)	1,657 (5.8)	4,592 (4.0)	
Chronic obstructive pulmonary disease†				<0.001
No	127,323 (89.6)	24,815 (87.4)	102,508 (90.1)	
Yes	14,824 (10.4)	3,588 (12.6)	11,236 (9.9)	
Depression†				<0.001
No	98,849 (69.5)	16,963 (59.7)	81,886 (72.0)	
Yes	43,298 (30.5)	11,440 (40.3)	31,858 (28.0)	
Diabetes†				<0.001
No	64,951 (45.7)	10,626 (37.4)	54,325 (47.8)	
Yes	77,196 (54.3)	17,777 (62.6)	59,419 (52.2)	
Chronic kidney failure†				<0.001
No	134,327 (94.5)	26,499 (93.3)	107,828 (94.8)	
Yes	7,820 (5.5)	1,904 (6.7)	5,916 (5.2)	
Neoplasm†				<0.001
No	96,901 (68.2)	16,748 (59.0)	80,153 (70.5)	
Yes	45,246 (31.8)	11,655 (41.0)	33,591 (29.5)	
Surgeries related to hypocalcaemia†,§				<0.001
No	141,328 (99.4)	28,173 (99.2)	113,155 (99.5)	
Yes	819 (0.6)	230 (0.8)	589 (0.5)	
Osteoporosis†				<0.001
No	73,753 (51.9)	2,075 (7.3)	71,678 (63.0)	
Yes	68,394 (48.1)	26,328 (92.7)	42,066 (37.0)	
Vitamin D deficiency†				<0.001
No	131,694 (92.6)	23,710 (83.5)	107,984 (94.9)	
Yes	10,453 (7.4)	4,693 (16.5)	5,760 (5.1)	
Corticosteroids†				<0.001
No	130,138 (91.5)	24,810 (87.3)	105,328 (92.6)	
Yes	12,009 (8.5)	3,593 (12.7)	8,416 (7.4)	
Drugs that could modify fracture risk†,#				<0.001
No	9,780 (6.9)	578 (2.0)	9,202 (8.1)	
Yes	132,367 (93.1)	27,825 (98.0)	104,542 (91.9)	
Periprosthetic joint infection				0.28
No	138,041 (97.1)	27,555 (97.0)	110,486 (97.1)	
Yes	4,106 (2.9)	848 (3.0)	3,258 (2.9)	

Data are mean (SD), median (IQR), Charlson Comorbidity Index score (SD) or n (%) unless otherwise specified.
Abbreviations: SD, standard deviation; IQR, interquartile range
† Time-dependent variables
* Values at baseline
§ Gastrectomy, thyroidectomy, and parathyroidectomy
# Proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, antiparkinsonism drugs, statins, thiazide diuretics, and anxiolytics

Table 2. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use

Calcium and vitamin D combination use	Number of events	Person-years	Adjusted hazard ratio[a]			
			No time-lag		6 months time-lag	
			95% CI	*p* value	95% CI	*p* value
No use	1,532	3,733	1.00 (REF)		1.00 (REF)	
Use	346	1,382	0.73 (0.61-0.87)	<0.001	0.56 (0.45-0.70)	<0.001
Total	1,878	5,115				

Abbreviations: CI, confidence interval; REF, reference

[a]The hazard ratios were adjusted for age, sex, type of insurance, Charlson Comorbidity Index, hospital region, comorbidities that are known to affect arthroplasty revision rate (chronic obstructive pulmonary disease, depression, diabetes, chronic kidney failure, neoplasm, and surgery related to hypocalcaemia), osteoporosis, vitamin D deficiency, corticosteroids, and other drugs that could also modify fracture risk (proton pump inhibitors, antiarrhythmics, anticonvulsants, antiparkinsonism drugs, statins, thiazide diuretics, and anxiolytics).

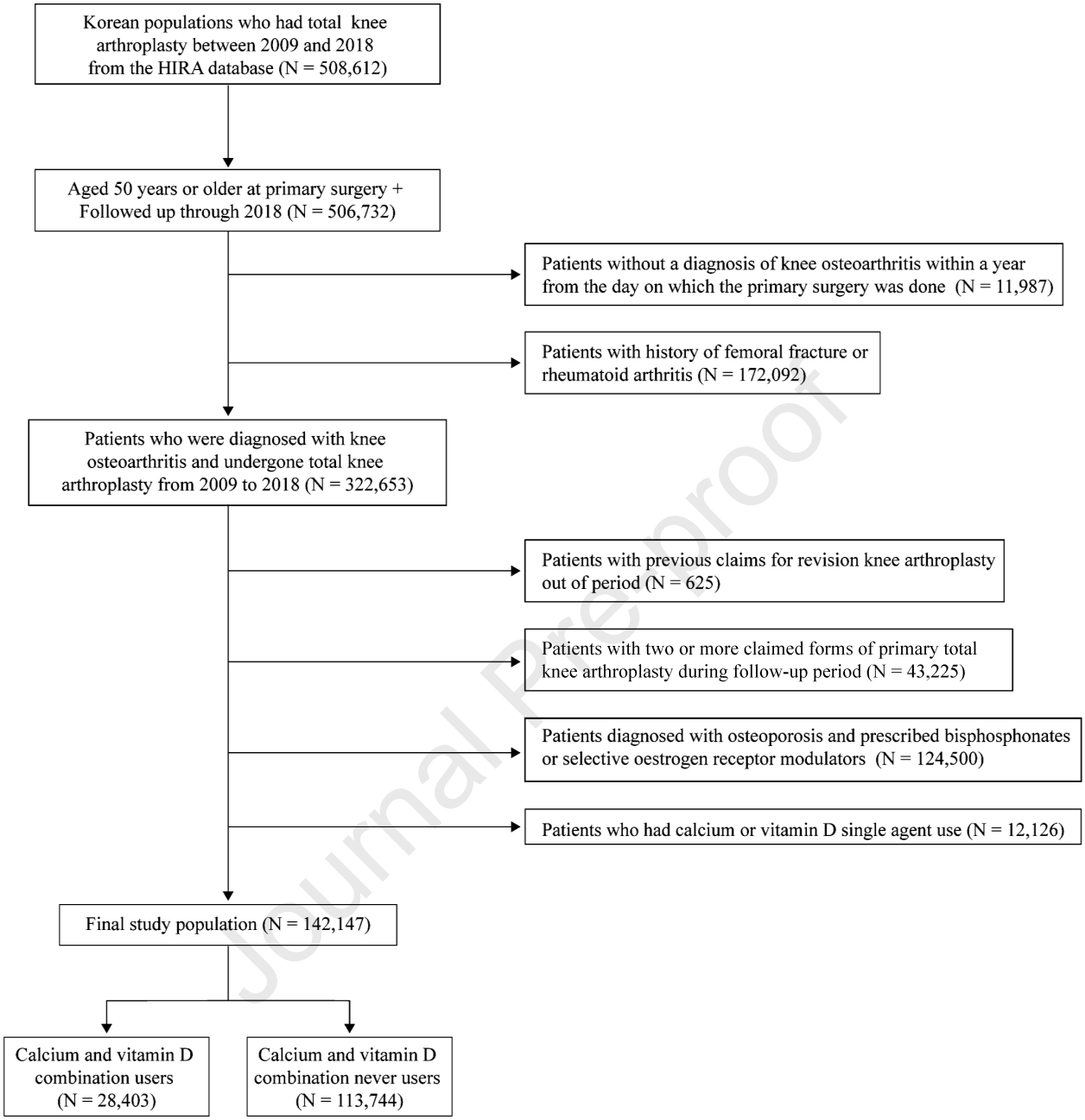
Table 3. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use by cumulative duration since primary operation according to infection (no time-lag, adjusted for confounders)

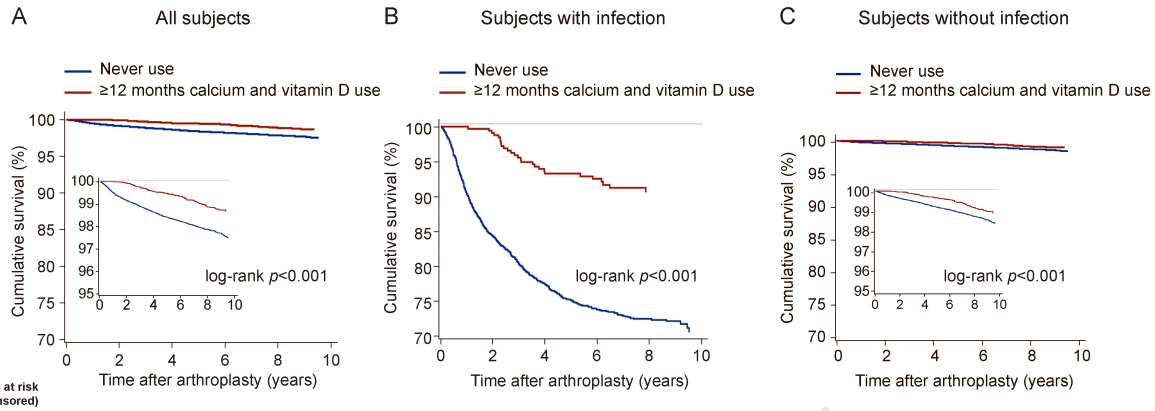
		All subjects				Subjects with infection[b]				Subjects without infection[b]			
		Number of events	Person-years	Adjusted hazard ratio[a] 95% CI	*p* value	Number of events	Person-years	Adjusted hazard ratio[a] 95% CI	*p* value	Number of events	Person-years	Adjusted hazard ratio[a] 95% CI	*p* value
Cumulative duration of use													
No use		1,532	3,733	1.00 (REF)		744	1,395	1.00 (REF)		788	2,338	1.00 (REF)	
Use	<12 months	251	942	0.96 (0.83-1.10)	0.54	97	285	0.99 (0.79-1.24)	0.96	154	657	1.03 (0.86-1.24)	0.76
	≥12 months	95	440	0.65 (0.52-0.81)	<0.001	27	95	0.63 (0.42-0.95)	0.03	68	345	0.70 (0.54-0.91)	0.008
Total		1,878	5,115			868	1,775			1,010	3,340		

Abbreviations: CI, confidence interval; REF, reference

[a]The hazard ratios were adjusted for age, sex, type of insurance, Charlson Comorbidity Index, hospital region, comorbidities that are known to affect arthroplasty revision rate (chronic obstructive pulmonary disease, depression, diabetes, chronic kidney failure, neoplasm, and surgery related to hypocalcaemia), osteoporosis, vitamin D deficiency, corticosteroids, and other drugs that could also modify fracture risk (proton pump inhibitors, antiarrhythmics, anticonvulsants, antiparkinsonism drugs, statins, thiazide diuretics, and anxiolytics).

[b]Statistically significant interaction effects were found for infection between patients who used calcium and vitamin D for less than 12 months and those who never use either; and between patients who used both for 12 months and longer and those who never use either (p=0.04, p=0.001)

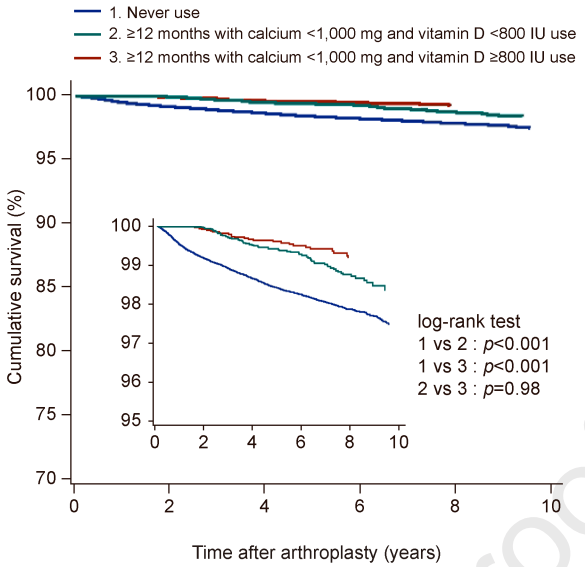




Numbers at risk (number censored)							
Never use	113,744 (0)	83,496 (29,413)	57,056 (55,488)	36,288 (76,055)	16,787 (95,460)	0 (112,212)	
≥12 months calcium and vitamin D use	12,007 (0)	11,377 (622)	9,399 (2,561)	7,110 (4,833)	3,871 (8,047)	0 (11,912)	

Numbers at risk (number censored)							
Never use	3,258 (0)	2,368 (408)	1,657 (947)	1,113 (1,421)	520 (1,999)	0 (2,514)	
≥12 months calcium and vitamin D use	331 (0)	321 (7)	273 (38)	225 (83)	127 (177)	0 (304)	

Numbers at risk (number censored)							
Never use	110,486 (0)	81,128 (29,005)	55,399 (54,541)	35,175 (74,634)	16,267 (93,461)	0 (109,698)	
≥12 months calcium and vitamin D use	11,676 (0)	11,506 (615)	9,126 (2,523)	6,885 (4,750)	3,774 (7,870)	0 (11,608)	



Numbers at risk (number censored)						
Never use	113,744 (0)	83,496 (29,413)	57,056 (55,488)	36,288 (76,055)	16,787 (95,460)	0 (112,212)
≥12 months with calcium <1,000 mg and vitamin D <800 IU use	6,472 (0)	6,218 (250)	5,332 (1,111)	4,125 (2,306)	2,358 (4,056)	0 (6,408)
≥12 months with calcium <1,000 mg and vitamin D ≥800 IU use	5,028 (0)	4,669 (355)	3,685 (1,354)	2,657 (2,351)	1312 (3,690)	0 (5,002)

Highlights

- Calcium and vitamin D use reduced the revision risk after total knee arthroplasty.
- The reduced revision risk was consistent regardless of periprosthetic joint infection.
- Implant survival was also significantly improved with calcium and vitamin D use.

The association of calcium and vitamin D use with implant survival of total knee arthroplasty: a nationwide population based cohort study

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Figure legends

Figure 1. Flowchart showing the selection process for users and never users of calcium and vitamin D combination

Figure 2. Log-rank tests with Kaplan-Meier survival analyses for revision events after primary total knee arthroplasty comparing cumulative duration of calcium and vitamin D combination use (never users vs. ≥12 months) in (A) all subjects, (B) subjects with infection, and (C) subjects without infection

Figure 3. Log-rank test with Kaplan-Meier survival analysis for revision events after primary total knee arthroplasty according to a mean daily dose of vitamin D with concomitant use of calcium (<1,000 mg) more than 1 year (never use vs. vitamin D ≥800 IU use vs. vitamin D <800 IU use)

Supplementary materials

Calcium and vitamin D use is associated with reduced revision rates of total knee arthroplasty both with and without infection: a nationwide population based cohort study

Supplemental Table 1. Definition of primary total knee arthroplasty and revision knee arthroplasty using healthcare common procedure coding system codes provided by HIRA

Supplemental Table 2. Prescription drugs codes based on health insurance claims payment coding system

Supplemental Table 3. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use (unadjusted for confounders)

Supplemental Table 4. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use by cumulative duration since primary operation (no time-lag)

Supplemental Table 5. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use by cumulative duration since primary operation and mean daily dose of each nutrient (no time-lag, all subjects)

Supplemental Table 6. Survival probability (%) of implants by time from primary operation

Supplemental Table 1. Definition of primary total knee arthroplasty and revision knee arthroplasty using healthcare common procedure coding system codes provided by HIRA

Type of surgery	Code in Healthcare Common Procedure
Primary total knee arthroplasty	N2072, N2077
Revision knee arthroplasty	N3712, N3717, N3722, N3727

Supplemental Table 2. Prescription drugs codes based on health insurance claims payment coding system

Drugs	Codes in health insurance claims payment
Calcium and vitamin D combination	302600ATB, 303200ATB, 387900ATB, 409100ATB, 462700ATB, 462800ATB, 473800ATB, 480200ATB, 498200ATB, 498300ATB, 503100ATB, 503500ATB, 504400ATB, 508700ATB, 519000ATB, 521900ATB, 526100ATB, 634000ATB, 665600ATB
Calcium or vitamin D single agents	104601ACS, 104601ATB, 104602ACS, 121401ACS, 121402ACS, 121601ACS, 121630BIJ, 121801ATB, 121901ATB, 122101ATB, 194602ATB, 205601ATB, 205602ATB, 207601ATB
Bisphosphonates	147401ATB, 207901ATB, 228301ATB, 228302ATB, 228303ALQ, 228303ATB, 228305ATB, 442301ATB, 442302ATB, 442302ATE, 442303ATB, 442330ATB, 468000ATE, 480304ATB, 481100ATB, 484001ATB, 500200ATB, 511200ATB, 518400ATB, 523900ATB, 487502BIJ, 207930BIJ, 420731BIJ, 420732BIJ, 480330BIJ, 646301BIJ
SERM (Selective estrogen receptor modulators)	136201ATB, 234501ATB, 234502ATB, 242101ATB, 358001ATB, 617101ATB

Supplemental Table 3. Crude risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use (unadjusted for confounders)

	Number of events	Person-years	Crude hazard ratio			
			No time-lag		6 months time-lag	
			95% CI	*p* value	95% CI	*p* value
Calcium and vitamin D combination use						
No use	1,532	3,733	1.00 (REF)		1.00 (REF)	
Use	346	1,382	1.06 (0.89-1.26)	0.54	0.80 (0.65-0.99)	0.04
Total	1,878	5,115				

Abbreviations: CI, confidence interval; REF, reference

Supplemental Table 4. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use by cumulative duration since primary operation (no time-lag)

		Number of events	Person-years	Crude hazard ratio		Adjusted hazard ratio[a]	
				95% CI	*p* value	95% CI	*p* value
Cumulative duration of use							
No use		1,532	3,733	1.00 (REF)		1.00 (REF)	
Use	<3 months	137	537	1.65 (1.40-1.95)	<0.001	1.09 (0.92-1.30)	0.31
	3 to <6 months	56	188	1.15 (0.85-1.55)	0.37	0.77 (0.57-1.04)	0.09
	6 to <12 months	58	217	1.24 (0.94-1.63)	0.12	0.82 (0.63-1.09)	0.17
	12 to <24 months	39	157	0.97 (0.70-1.34)	0.85	0.66 (0.48-0.91)	0.01
	≥24 months	56	283	0.91 (0.69-1.20)	0.49	0.64 (0.49-0.85)	0.002
Total		1,878	5,115				

Abbreviations: CI, confidence interval; REF, reference

[a] The hazard ratios were adjusted for age, sex, type of insurance, Charlson Comorbidity Index, hospital region, comorbidities that are known to affect arthroplasty revision rate (chronic obstructive pulmonary disease, depression, diabetes, chronic kidney failure, neoplasm, and surgery related to hypocalcaemia), osteoporosis, vitamin D deficiency, corticosteroids, and other drugs that could also modify fracture risk (proton pump inhibitors, antiarrhythmics, anticonvulsants, antiparkinsonism drugs, statins, thiazide diuretics, and anxiolytics).

Supplemental Table 5. Risks for revision of primary total knee arthroplasty associated with calcium and vitamin D combination use by cumulative duration since primary operation and mean daily dose of each nutrient (no time-lag, all subjects)

				All subjects					
				Number of events	Person-years	Crude hazard ratio		Adjusted hazard ratio[a]	
						95% CI	*p* value	95% CI	*p* value
Cumulative duration of use									
No use				1,532	3,733	1.00 (REF)		1.00 (REF)	
Use	<12 months	All doses		251	942	1.44 (1.26-1.65)	<0.001	0.96 (0.83-1.10)	0.54
	≥12 months	All doses		95	440	0.93 (0.75-1.15)	0.51	0.65 (0.52-0.81)	<0.001
Cumulative duration and mean daily dose									
No use				1,532	3,733	1.00 (REF)		1.00 (REF)	
Use	<12 months	All doses		251	942	1.44 (1.26-1.65)	<0.001	0.96 (0.83-1.10)	0.54
	≥12 months	Calcium ≥1,000 mg	Vitamin D ≥800 IU	3	16	0.52 (0.13-2.01)	0.36	0.38 (0.10-1.54)	0.18
			Vitamin D <800 IU	2	11	2.01 (0.50-8.03)	0.33	1.47 (0.37-5.88)	0.59
		Calcium <1,000 mg	Vitamin D ≥800 IU	26	105	0.70 (0.48-1.04)	0.07	0.49 (0.33-0.73)	<0.001
			Vitamin D <800 IU	64	308	1.08 (0.84-1.40)	0.54	0.75 (0.58-0.98)	0.03
Total				1,878	5,115				

				All subjects					
				Number of events	Person-years	Crude hazard ratio		Adjusted hazard ratio[a]	
						95% CI	*p* value	95% CI	*p* value
Cumulative duration and mean daily dose									
No use				1,532	3,733	1.00 (REF)		1.00 (REF)	
Use	<12 months	All doses		251	942	1.44 (1.26-1.65)	<0.001	0.96 (0.83-1.10)	0.54
	≥12 months	Calcium ≥1,000 mg	Vitamin D ≥400 IU	5	27	0.93 (0.37-2.35)	0.88	0.68 (0.27-1.73)	0.42
			Vitamin D <400 IU	0	0	ND	ND	ND	ND
		Calcium <1,000 mg	Vitamin D ≥400 IU	81	368	0.99 (0.79-1.25)	0.95	0.69 (0.55-0.87)	0.002
			Vitamin D <400 IU	9	45	0.67 (0.35-1.28)	0.22	0.47 (0.25-0.89)	0.02
Total				1,878	5,115				

Abbreviations: CI, confidence interval; REF, reference; ND, not done because of insufficient number of events

[a] The hazard ratios were adjusted for age, sex, type of insurance, Charlson Comorbidity Index, hospital region, comorbidities that are known to affect arthroplasty revision rate (chronic obstructive pulmonary disease, depression, diabetes, chronic kidney failure, neoplasm, and surgery related to hypocalcaemia), osteoporosis, vitamin D deficiency, corticosteroids, and other drugs that could also modify fracture risk (proton pump inhibitors, antiarrhythmics, anticonvulsants, antiparkinsonism drugs, statins, thiazide diuretics, and anxiolytics).

Supplemental Table 6. Survival probability (%) of implants by time from primary operation

		1 YR	2 YRS	3 YRS	4 YRS	5 YRS	6 YRS	7 YRS	8 YRS	9 YRS
All subjects	Never Users	99.50	99.16	98.90	98.65	98.42	98.23	98.05	97.88	97.70
	Calcium and vitamin D use (≥12 months)	100	99.93	99.74	99.56	99.48	99.35	99.17	98.87	98.73
	Improvement of implant failure rate*	100	91.67	76.36	67.41	67.09	63.28	57.44	46.70	44.78
	Calcium <1,000 mg and vitamin D <800 IU use (≥12 months)	100	99.94	99.69	99.51	99.41	99.41	99.26	99.02	98.71
	Calcium <1,000 mg and vitamin D ≥800 IU use (≥12 months)	100	99.92	99.78	99.63	99.60	99.50	99.42	99.17	ND
Subjects with infection	Never Users	90.39	84.42	80.41	77.53	75.25	73.85	73.06	72.56	72.22
	Calcium and vitamin D use (≥12 months)	100	99.08	95.62	93.64	93.30	92.54	91.24	90.57	ND
	Improvement of implant failure rate*	100	94.09	77.64	71.70	72.9	71.47	67.48	65.63	ND
Subjects without infection	Never Users	99.78	99.64	99.50	99.35	99.20	99.06	98.91	98.75	98.58
	Calcium and vitamin D use (≥12 months)	100	99.96	99.86	99.74	99.67	99.56	99.42	99.14	98.99
	Improvement of implant failure rate*	100	88.89	72.00	60.00	58.8	53.19	46.79	31.20	28.87

Abbreviations: YRS, years; ND, not done because of insufficient number of events
*Improvement of implant failure rate = Difference in implant failure rate (rates in users – rates in never users) / implant failure rate in never users x 100(%)