Research Article

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A biochemical perspective on bone-implant interface healing after cemented knee arthroplasty: role of serum calcium and ALP

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Abstract

Objectives: Osteointegration at the bone-cement interface is essential for the long-term success of implants following cemented total knee arthroplasty (TKA). This study aims to assess the time-dependent changes in serum calcium (Ca) and alkaline phosphatase (ALP) levels after TKA and to explore their relationship with functional recovery and osteointegration potential.

Methods: This prospective study involved 100 patients who underwent primary cemented TKA. Serum Ca and ALP levels were measured before surgery and at postoperative days 1, 3 weeks, 6 weeks, 6 months, and 1 year. Functional outcomes were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), while pain levels were recorded with a 10-point Visual Analog Scale (VAS). Knee range of motion (ROM) was measured with a goniometer. Correlation and multivariate regression analyses were conducted to assess links between biochemical markers and clinical outcomes. Radiographic osteolysis was evaluated through standard X-rays.

Results: Serum Ca levels significantly declined over time ($p<0.001$), while ALP showed a biphasic pattern. Clinical outcomes, including WOMAC, VAS, and ROM, improved markedly (all $p<0.001$). However, no significant correlations were observed between Ca or ALP levels and these outcomes (all $p>0.05$).

Conclusions: Although measurable changes in serum calcium and ALP levels are observed following cemented TKA, these parameters demonstrate limited clinical utility as systemic markers of osteointegration or predictors of functional recovery. is warranted to assess implant integration and postoperative bone healing better.

Keywords: knee arthroplasty; calcium; alkaline phosphatase; osteointegration

Introduction

Total knee arthroplasty (TKA) is a widely utilized and effective surgical intervention for advanced knee osteoarthritis and other degenerative joint disorders, aiming to reduce pain, increase joint range of motion, and improve overall quality of life [1, 2]. The long-term success of TKA depends not only on accurate anatomical placement of the prosthetic components but also on the quality of the periprosthetic bone bed that supports them [3, 4]. The durability of the implant is closely linked to the bone's ability to maintain its microstructural integrity and mineral density over time [5–7].

Cemented fixation, commonly preferred in modern TKA procedures, is achieved using polymethylmethacrylate (PMMA)-based bone cement. This method enhances primary implant stability and facilitates optimal mechanical performance by ensuring homogeneous load transfer across the bone-cement interface [8]. Notably, the penetration depth and uniformity of the cement layer play a decisive role in

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both short- and long-term prosthetic stability [9, 10]. However, over time, this interface is subjected to biomechanical stresses and biological remodeling processes [11]. Factors such as abnormal joint loading, mechanical axis deviation, or variations in surgical technique can compromise the integrity of the cement-bone interface, thereby affecting implant stability [12].

The capacity for remodeling and microstructural endurance of the periprosthetic bone bed is therefore critical to sustaining long-term osteointegration [13]. Systemic biochemical markers of bone metabolism can be employed to monitor the biological changes occurring in the periprosthetic environment [14]. Among these, serum calcium (Ca) concentration and alkaline phosphatase (ALP) activity are key biomarkers reflecting the balance between bone formation and resorption [15]. A decrease in serum Ca may indicate inadequate mineralization and compromised osteointegration, whereas elevated ALP acitivities may reflect increased bone turnover, potentially associated with poor bone quality and a higher risk of periprosthetic complications [16].

Consequently, abnormal Ca or ALP levels may be linked to delayed cement-bone union and impaired implant stabilization. In contrast, physiologically normal Ca levels and balanced ALP activity may support faster and more robust osteointegration [17]. Yet, it remains unclear whether common biochemical markers like Ca and ALP can reflect osteointegration progress.

In this study, we aimed to evaluate the preoperative and postoperative changes in serum Ca and ALP levels in patients undergoing primary cemented TKA. Additionally, we sought to investigate the potential associations of these biochemical markers with bone–cement interface stability, clinical functional outcomes, and radiological indicators of osteointegration.

Materials and methods

This single-center, prospective observational study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of the local ethics committee (Approval No: İ06-532-25). Clinical, biochemical and radiological data of 100 patients who underwent primary cemented total knee arthroplasty (TKA) in the Orthopedics and Traumatology Clinic of our hospital between December 2022 and December 2024 and were followed up regularly for at least 12 months postoperatively were evaluated.

Demographic data such as age, gender and systemic diseases were recorded. Inclusion criteria were as follows: advanced primary gonarthrosis (Kellgren-Lawrence stage III-IV) refractory to conservative treatment, surgical indication approved by two experienced orthopedic surgeons, no bilateral involvement, preoperative knee flexion angle ≥70°, and deformity <15° in the frontal plane. Exclusion criteria included age below 60 years, history of previous knee surgery, need for revision arthroplasty, known or suspected metal allergy, systemic rheumatic disease, active infection, significant serum calcium or ALP elevation in the preoperative period, metabolic bone diseases, and failure to give informed consent.

All surgical procedures were performed by experienced orthopedic surgeons using a medial parapatellar approach. Femoral and tibial components were fixed with antibiotic polymethylmethacrylate (PMMA) based bone cement. Patella resurfacing was not performed.

In the postoperative period, patients were mobilized with full weight bearing from the first day and were subjected to a standard rehabilitation protocol including continuous passive motion (CPM). Patients were called for outpatient visits at 3 weeks, 6 weeks, 6 months and 1 year.

Clinical evaluations were performed preoperatively and at 1 year postoperatively. Functional outcomes were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); pain level was measured with a Visual Analog Scale (VAS) scored from 0 to 10. Knee range of motion (ROM) was determined with a goniometer. WOMAC and VAS scores were collected independently by two different clinicians and WOMAC questionnaires were completed individually by the patients.

Radiological evaluations were performed on weight-bearing anteroposterior (AP) and lateral knee radiographs obtained at 6 weeks, 6 months and 1 year postoperatively. Femoral and tibial component circumferences were divided into zones (medial/lateral and anterior/posterior zones) according to the Knee Society Radiologic Evaluation System. Radiolucent lines, osteolytic lesions, component alignment and position changes were evaluated. Radiolucent lines >2 mm in width and increasing over time were considered in favor of osteolysis; stable lines smaller than 2 mm were considered clinically insignificant. Radiologic osteointegration was defined as the preservation of continuous bone attachment around the component and the absence of signs of aseptic loosening. All radiological evaluations were performed independently by two experienced orthopedists; no disagreement was reported.

For the biochemical evaluation, serum total calcium (Ca) and ALP activities were measured preoperatively and on postoperative day 1, weeks 3, weeks 6, months 6, and year 1 from morning fasting blood samples. Ca levels were analyzed by the Ca-Arsenazo III method and ALP activities were analyzed by the IFCC-recommended enzymatic kinetic

method, measuring the conversion rate of p-nitrophenyl phosphate (pNPP) to p-nitrophenol (pNP) in the presence of magnesium and zinc ions and of 2-amino-2-methyl-1-propanol (AMP) as a phosphate acceptor at pH 10.4.

Serum samples were freshly collected from patients at each scheduled control time point (preoperative, postoperative day 1, week 3, week 6, month 6, and year 1) and analyzed on the same day between 08:00 and 09:00 a.m.; no samples were stored. All biochemical measurements, including serum calcium (Ca) and alkaline phosphatase (ALP) levels, were performed in the same laboratory using a Beckman Coulter AU5800 analyzer (Beckman Coulter Inc., Brea, CA, USA) and standardized IFCC reference methods to ensure analytical consistency. The intra-assay and inter-assay coefficients of variation were <2.5 % and <4.5 %, respectively. ALP was evaluated as a biochemical indicator of osteoblastic activity and serum Ca levels as a marker of general bone metabolism and potential resorptive processes.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics v25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov–Smirnov test, and normally distributed data were presented as mean±standard deviation. Biochemical parameters that changed over time were analyzed by repeated measures ANOVA. Differences between preoperative and postoperative clinical scores were compared using the paired samples t-test.

Correlations between biochemical parameters (serum calcium and alkaline phosphatase levels) and clinical outcomes (WOMAC, VAS, and ROM scores) were assessed using Pearson or Spearman correlation coefficients, depending on the distribution of variables.

To evaluate the predictive potential of biochemical parameters for postoperative clinical outcomes, multiple linear regression analyses were performed using serum calcium and ALP levels as independent variables. No additional covariates were included in the model. The assumptions of linearity, normality, homoscedasticity, and multicollinearity were verified prior to regression analyses. For all statistical tests, a p-Value <0.05 was considered statistically significant.

Results

In this study, 100 patients who underwent total knee arthroplasty (TKA) were evaluated. There were 80 females (80 %) and 20 males (20 %) with a mean age of 68.78 ± 5.26 years. Clinical evaluations were performed only in the preoperative period and at 1 year postoperatively, while biochemical evaluations were performed at five different time points: postoperative day 1, weeks 3, weeks 6, months 6 and year 1.

Statistically significant improvements were observed in all parameters in clinical evaluations between preoperative and postoperative 1st year. While the mean WOMAC score was 56.5 ± 8.6 in the preoperative period, this value increased to 78.8 ± 8.6 at the end of the 1st postoperative year ($p<0.001$). The VAS score evaluating the pain level was 7.5 ± 1.4 in the preoperative period and decreased significantly to 2.0 ± 0.5 at 1 year ($p<0.001$). Range of motion (ROM) increased from 93.8 ± 6.4° in the preoperative period to 113.5 ± 2.5° in the first postoperative year ($p<0.001$) (Table 1).

Biochemical evaluations showed that serum calcium (Ca) levels decreased gradually and significantly in the postoperative period. The mean Ca level was 9.39 ± 0.56 mg/dL preoperatively, decreased to 9.20 ± 0.54 mg/dL at day 1, 9.01 ± 0.48 mg/dL at week 3, 8.96 ± 0.47 mg/dL at week 6, 8.95 ± 0.53 mg/dL at month 6 and 8.83 ± 0.62 mg/dL at year 1. One-way analysis of variance (ANOVA) showed that this change was statistically significant ($p<0.001$). In post hoc analyses, the differences between preoperative Ca levels and all time points, including postoperative year 1 were significant (all $p<0.01$) (Table 2).

Serum alkaline phosphatase (ALP) levels increased from a mean of 112.61 ± 47.85 IU/L preoperatively to 137.11 ± 67.16 IU/L on postoperative day 1, followed by 115.40 ± 31.01 IU/L at 3 weeks, 122.32 ± 62.73 IU/L at 6 weeks, 111.94 ± 60.11 IU/L at 6 months, and 117.60 ± 34.75 IU/L at 1 year. ALP changes were significant over time (ANOVA $p=0.009$). In post hoc (multiple comparisons) analyses, no significant differences were found between preoperative ALP levels and postoperative day 1, week 6 and year 1 values (all $p>0.05$) (Table 2).

Table 1: Clinical outcome scores before and after surgery comparison of WOMAC, VAS, and ROM scores between preoperative and postoperative 1-year evaluations.

Score	Preoperative (mean ± SD)	Postoperative 1st year (mean ± SD)	p-Value
WOMAC	56.5 ± 8.6	78.8 ± 8.6	<0.001
VAS	7.5 ± 1.4	2.0 ± 0.5	<0.001
ROM	93.8 ± 6.4	113.5 ± 2.5	<0.001

WOMAC, western ontario and mcMaster universities osteoarthritis index; VAS, visual analog scale; ROM, range of motion. A p-value <0.05 was considered statistically significant.

Table 2: Serum calcium (Ca) and alkaline phosphatase (ALP) levels at follow-up points biochemical marker trends measured at 1st day, 3rd week, 6th week, 6th month, and 1st year postoperatively.

	Time						
	Preoperative	**Postop day 1**	**Postop week 3**	**Postop week 6**	**Postop month 6**	**Postop year 1**	**ANOVA p-value**
Ca, mg/dL, mean ± SD	9.33 ± 0.51	9.20 ± 0.54	9.01 ± 0.48	8.96 ± 0.47	8.95 ± 0.53	8.83 ± 0.62	0.000038
ALP, IU/L, mean ± SD	110.74 ± 43.08	137.11 ± 67.16	115.40 ± 31.01	122.32 ± 62.73	111.94 ± 60.11	117.60 ± 34.75	0.009

Ca, calcium; ALP, alkaline phosphatase. A p-value <0.05 was considered statistically significant.

At the 1-year follow-up, no significant correlations were observed between serum calcium (Ca) or alkaline phosphatase (ALP) levels and clinical outcomes, including WOMAC, VAS, and ROM scores. Both Pearson and Spearman correlation analyses showed weak, non-significant associations (all $p>0.20$). Similarly, multiple linear regression analyses indicated that Ca and ALP levels were not significant predictors of postoperative functional or pain-related outcomes (all $p>0.30$). Overall, these findings suggest that serum Ca and ALP levels are not associated with postoperative clinical recovery.

In radiologic evaluations, anteroposterior (AP) and lateral knee radiographs were taken in the weight-bearing position on postoperative day 1, week 6, month 6 and year 1. No osteolysis was found in any of the patients.

Discussion

This study aimed to comprehensively evaluate postoperative changes in serum calcium (Ca) and alkaline phosphatase (ALP) levels in patients undergoing total knee arthroplasty (TKA), and to investigate their relationship with osteointegration at the cement–bone interface from both clinical and radiological perspectives. The findings revealed a statistically significant decline in serum Ca levels and a fluctuating trend in ALP levels throughout the postoperative period. However, these biochemical parameters were not significantly correlated with functional outcomes (WOMAC, VAS, ROM) or radiographic evidence of osteointegration.

Ca and ALP are two essential biomarkers in bone metabolism. Calcium plays a critical role in osteoblastic regulation and is a fundamental element of mineralization, while ALP is an enzymatic marker involved in calcium-phosphate deposition on the osteoid matrix [18]. The progressive decline in serum Ca levels observed in our study may reflect a physiological response to increased osteoblastic activity and the incorporation of Ca into the maturing bone matrix. Meanwhile, the initial rise in ALP at postoperative day 1, followed by a decline at six months and a subsequent increase at one year, represents a dynamic progression of osteoblastic phases. This temporal profile reflects the phased nature of post-implant remodeling and is consistent with previously described biological patterns involving early osteoblastic stimulation and later stabilization [19, 20].

However, the time-dependent variations in Ca and ALP levels were not significantly associated with clinical functional recovery (WOMAC, VAS, ROM) or radiological indicators of osteointegration, suggesting that these markers do not directly reflect the osteointegration process. Our findings support the view that systemic biochemical markers may not fully capture the localized biological healing occurring at the bone-cement interface, and that osteointegration is a multifactorial process influenced by both biological and mechanical factors.

Furthermore, calcium homeostasis and ALP activity are tightly regulated by systemic hormonal factors such as parathyroid hormone (PTH) and 25(OH) vitamin D [18]. Fluctuations in these regulatory pathways may influence postoperative bone metabolism and the remodeling response following total knee arthroplasty, even when conventional biochemical markers such as Ca and ALP remain within physiological ranges.

The absence of radiographic osteolysis in our cohort suggests that the observed decline in serum Ca represents a physiological, rather than pathological, adaptation. Osteolysis is typically associated with wear particle-induced inflammation, cytokine release, and increased osteoclastic activity [21]. The observed ALP pattern – indicative of ongoing remodeling rather than destructive osteolytic processes – combined with Ca levels that remained within physiologic ranges, supports a favorable periprosthetic remodeling response [22]. These biochemical trends may be interpreted as indirect evidence of successful early osteointegration in cemented TKA [23, 24].

However, correlation analyses failed to demonstrate significant associations between Ca and ALP levels and clinical functional outcomes, suggesting that these markers are poor predictors of clinical recovery. This reinforces the notion that systemic biomarkers may be limited in their ability to reflect localized biological events such as osteointegration. Furthermore, clinical outcomes after TKA are

influenced by a complex array of factors, including surgical technique, patient age, biomechanics, rehabilitation protocols, and individual motivation [25, 26].

More specific bone turnover markers – such as P1NP, osteocalcin, CTX, and TRAP-5b – may offer improved biochemical monitoring of osteoblastic and osteoclastic activity [27, 28]. Nevertheless, their routine use in clinical practice is hindered by high costs and limited laboratory availability. In contrast, markers like Ca and ALP are inexpensive, widely available, and easy to measure [29, 30]. Despite these advantages, our findings demonstrate that they lack the sensitivity and specificity required to effectively monitor osteointegration or predict functional recovery [31].

This study has certain limitations. Notably, the absence of direct evaluations of the local bone microenvironment – such as bone biopsies, periprosthetic fluid analysis, or advanced imaging modalities like micro-CT – limits the granularity of interpretation. Additionally, the inability to differentiate ALP isoenzymes prevented assessment of bone-specific ALP activity. Serum 25(OH) vitamin D and parathyroid hormone (PTH) levels were not measured, as these parameters are not routinely included in our institution's postoperative biochemical panel; this may represent a limitation of the study. Despite these limitations, the prospective study design, homogeneous patient population, predefined follow-up intervals, and blinded radiologic assessments by experienced orthopedic surgeons represent key strengths.

Conclusions

In this study, significant time-dependent variations in serum calcium (Ca) and alkaline phosphatase (ALP) levels were observed after total knee arthroplasty (TKA); however, these biochemical markers showed no significant correlation with clinical recovery parameters (WOMAC, VAS, ROM) or radiological indicators of osteointegration. These findings suggest that although Ca and ALP reflect general bone metabolism, they are insufficient to predict or monitor osteointegration. Osteointegration is a multifactorial process influenced by local mechanical and biological factors rather than systemic biochemical changes. Further studies using more specific bone turnover biomarkers in larger cohorts are warranted to establish reliable biochemical tools for postoperative monitoring.

Research ethics: Date: 17/07/2025 We obtained ethical approval (No. İ5-279-20).
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