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ORIGINAL ARTICLE

Role of Serum Alkaline Phosphatase and Osteocalcin in Predicting Bone Healing after Internal Fixation of Long Bone Fractures

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ABSTRACT

Background: Bone healing is a complex biological process that depends on coordinated cellular and biochemical mechanisms. Traditional radiographic evaluation often fails to reflect early biological healing. Therefore, biochemical markers such as serum alkaline phosphatase (ALP) and osteocalcin (OC) may serve as valuable indicators of osteoblastic activity and bone regeneration. This study aimed to assess the predictive role of ALP and OC in monitoring bone healing following internal fixation of long bone fractures.

Methods: A prospective observational study was conducted from June 2022 to May 2023 at the Department of Orthopedic Surgery, Social Security Hospital, Shahdara, Lahore, in collaboration with the Department of Radiology, Gambat Institute of Medical Sciences, Sindh. A total of 150 patients aged 18–65 years with long bone fractures managed by internal fixation were included. Serum ALP and OC levels were measured preoperatively and at 4, 8, and 12 weeks postoperatively. Radiographic healing was evaluated using the Radiographic Union Scale for Tibial fractures (RUST), and correlations between biochemical markers and healing scores were analyzed.

Results: Both ALP and OC levels increased significantly during the healing period ($p < 0.001$). ALP peaked at 8 weeks (129.7 ± 18.8 IU/L), while OC showed a steady rise up to 12 weeks (28.7 ± 7.1 ng/mL). Osteocalcin demonstrated a stronger correlation with RUST scores ($r = 0.72$, $p < 0.001$) than ALP ($r = 0.66$, $p < 0.01$). Patients with higher OC and ALP values showed faster and more complete union at 12 weeks.

Conclusion: Serial measurement of serum ALP and osteocalcin provides a reliable, non-invasive method to predict and monitor bone healing following internal fixation of long bone fractures, with osteocalcin serving as a more sensitive marker of late-stage bone formation.

Keywords: Alkaline phosphatase, Osteocalcin, Bone healing, Internal fixation, Long bone fractures, Biochemical markers.

INTRODUCTION

Fracture healing is a complex and dynamic physiological process involving the interplay of cellular, biochemical, and mechanical factors that work together to restore bone structure and function[1]. Long bone fractures, including those of the femur, tibia, and humerus, are among the most common orthopedic injuries seen in clinical practice. These injuries contribute significantly to morbidity, long-term disability, and socioeconomic burden, particularly in developing countries where trauma is a leading cause of hospitalization. The standard treatment for such fractures is internal fixation using metallic implants such as plates, screws, or intramedullary nails, which provide mechanical stability and promote biological healing. Despite advancements in surgical techniques, delayed union and non-union remain common complications, emphasizing the need for early and reliable indicators of bone healing[2,3].

Bone healing after internal fixation occurs through three overlapping stages namely the inflammatory, reparative, and remodeling phases. During these stages, osteogenic cells and bone-forming proteins coordinate to regenerate new bone tissue[4]. Traditionally, the assessment of fracture healing has relied on radiological methods such as plain X-rays or computed tomography scans. However, radiographic evaluation often detects healing only at later stages when substantial callus formation and mineralization have already occurred. Early biochemical changes reflecting bone cell activity and matrix formation remain undetectable by imaging. Therefore, the measurement of biochemical markers that mirror bone metabolism can provide valuable, non-invasive, and earlier insight into the healing process[5].

Among the biochemical indicators of osteoblastic activity, serum alkaline phosphatase (ALP) and osteocalcin (OC) are two of the most specific and reliable markers. Alkaline phosphatase is an enzyme secreted by osteoblasts during the early phase of bone formation[6]. It plays a crucial role in mineralization by hydrolyzing organic phosphate esters and promoting calcium and phosphate deposition into the bone matrix. Elevated ALP levels in serum typically indicate active bone formation, particularly during the early phase of callus development following a fracture. On the other hand, osteocalcin also known as bone gamma-carboxyglutamic acid-containing protein (BGLAP) is synthesized by mature osteoblasts and reflects later stages of bone formation. Osteocalcin binds to hydroxyapatite and regulates crystal growth within the matrix, serving as a sensitive indicator of bone turnover and remodeling[7].

Several studies have explored these biochemical markers in metabolic bone diseases such as osteoporosis and Paget's disease, but their predictive value in post-fracture bone healing is still being established[8]. Early identification of delayed or impaired bone union is crucial for timely intervention, as biochemical markers may reflect osteoblastic activity long before radiographic signs become apparent. Monitoring serum ALP and osteocalcin at different postoperative intervals could therefore serve as an adjunctive tool to radiographic assessment, allowing clinicians to evaluate the biological progression of fracture repair[9].

The present study was designed to evaluate the role of serum alkaline phosphatase and osteocalcin in predicting bone healing after internal fixation of long bone fractures. By correlating changes in these biochemical markers with radiological findings, the study aims to determine their diagnostic and prognostic significance. Establishing these markers as reliable indicators of bone healing could enhance postoperative monitoring, guide rehabilitation timelines, and assist in identifying patients at risk for delayed or non-union, thereby improving overall treatment outcomes in orthopedic practice[10,11].

MATERIALS AND METHODS

This prospective observational study was conducted in collaboration between the Department of Orthopedic Surgery at Social Security Hospital, Shahdara, Lahore, and the Department of Radiology at Gambat Institute of Medical Sciences (GIMS), Sindh. Patient enrollment and perioperative care were carried out at Social

Security Hospital, while all radiologic assessments were centralized and read at GIMS to ensure blinded, standardized scoring. The study period extended from June 2022 through May 2023. Adults aged 18–65 years presenting with acute, closed diaphyseal fractures of long bones (femur, tibia, or humerus) and managed with internal fixation (locking plate or intramedullary nail) were screened for eligibility. Exclusion criteria were open Gustilo–Anderson grade III injuries, pathological or periprosthetic fractures, polytrauma with head injury or hemodynamic instability, chronic kidney or liver disease, known metabolic bone disease, malignancy, current pregnancy or lactation, long-term corticosteroid or antiresorptive therapy, active infection at the fracture site, and inability to comply with follow-up. After informed written consent, a consecutive series of 150 patients meeting criteria were enrolled, reflecting the a priori sample size target based on detecting a moderate correlation ($r \approx 0.30$) between biochemical markers and radiographic healing with 80% power and $\alpha=0.05$, allowing for up to 10% attrition.

All operations were performed by consultant orthopedic surgeons following institutional protocols. Standard perioperative antibiotics and thromboprophylaxis were given as indicated, and postoperative rehabilitation followed a unified pathway specifying protected weight-bearing for lower-limb fractures and early range-of-motion for upper-limb fractures. Demographic and clinical variables were recorded at baseline, including age, sex, body mass index, smoking status, diabetes mellitus, fracture bone and side, fracture pattern, time to surgery, fixation method, and intraoperative details. Pain control, early complications, and compliance with rehabilitation were documented at each visit. The primary biochemical exposures were total serum alkaline phosphatase (ALP) and serum osteocalcin (OC). Venous blood was sampled preoperatively (within 24 hours before surgery) and postoperatively at 4, 8, and 12 weeks, with an additional sample at week 16 when clinically indicated. ALP was quantified on an automated analyzer using the International Federation of Clinical Chemistry (IFCC) kinetic method at 37 °C; OC was measured using a sandwich ELISA validated for human osteocalcin. All assays were run in duplicate; two-level internal quality controls were processed with each batch, and coefficients of variation were maintained below 5% for ALP and below 8% for OC. Samples from the same patient were processed in the same assay run whenever feasible to minimize inter-batch variation.

Radiographic healing was assessed with standardized anteroposterior and lateral views obtained at 4, 8, 12, and 16 weeks and then as clinically indicated until union or study end. De-identified images were transferred to GIMS for blinded review by two fellowship-trained musculoskeletal radiologists who independently scored healing using the Radiographic Union Scale for Tibial fractures (RUST) adapted to the relevant long bone. Disagreements were resolved by consensus; inter-rater reliability was quantified with the intraclass correlation coefficient. The primary radiologic endpoint was union at 12 weeks, defined a priori as RUST ≥ 10 with bridging callus across at least three cortices and no implant failure; time to union (weeks) was recorded as a secondary endpoint, alongside delayed union (lack of union by 24 weeks or need for secondary procedure). Clinical endpoints included pain on weight-bearing or functional use and presence of mechanical tenderness at the fracture site.

Data were entered into a locked electronic database with range and logic checks; missing values were minimized through immediate query resolution and handled analytically by multiple imputation if exceeding 5% for any variable. Continuous data are reported as mean ± standard deviation or median (interquartile range) as appropriate; categorical data are summarized as counts and percentages. Longitudinal trajectories of ALP and OC were analyzed with linear mixed-effects models including random intercepts for patients and fixed effects for time, adjusted for age, sex, diabetes, smoking, fracture location, and fixation type. Associations between biomarkers and radiographic healing were evaluated with Pearson or Spearman correlation and with multivariable linear regression for RUST at 12 weeks. Predictive performance for union at 12 weeks was examined using receiver operating characteristic (ROC) analysis with area under the curve (AUC), optimal cut-offs by Youden index, and internal validation via bootstrap resampling (1000 iterations). Pre-specified subgroup analyses compared lower-limb versus upper-limb fractures and plate versus nail fixation. Statistical significance was set at two-sided $p<0.05$. Analyses were performed using SPSS v26 and R v4.3. Ethical approval was obtained from the Institutional Review Boards of Social Security Hospital, Shahdara, Lahore, and Gambat Institute of Medical Sciences; the study adhered to the Declaration of Helsinki, and all participants provided written informed consent.

RESULTS

A total of 150 patients fulfilled the inclusion criteria and successfully completed the follow-up period. The mean age of the participants was 38.2 ± 11.6 years, with a male predominance (102 males, 68%) compared to females (48 females, 32%). The most commonly affected long bone was the femur (46%), followed by the tibia (38%) and humerus (16%). Road traffic accidents were the major cause of injury (62%), followed by falls (28%) and other minor traumas (10%). Among fixation methods, 58% of patients underwent plate fixation, while 42% were treated with intramedullary nailing. The baseline demographic and clinical features are summarized in Table 1.

As shown in Table 1, the majority of fractures involved weight-bearing bones (femur and tibia), which reflects the mechanical stress and kinetic energy transfer common in road traffic injuries. Only a small fraction of cases involved humeral fractures, which usually resulted from low-velocity trauma. Serial measurements of serum alkaline phosphatase (ALP) and osteocalcin (OC) demonstrated distinct temporal trends following internal fixation. Both markers increased significantly during the postoperative period, indicating progressive osteoblastic activation and bone matrix formation. The mean ALP level rose from 82.4 ± 13.9 IU/L preoperatively to 129.7 ± 18.8 IU/L at 8 weeks, then slightly declined at 12 weeks (122.5 ± 17.5 IU/L), suggesting early peak activity during callus mineralization. In contrast, osteocalcin increased steadily throughout the healing process, from 14.8 ± 5.1 ng/mL preoperatively to 28.7 ± 7.1 ng/mL at 12 weeks, representing continuous bone matrix maturation. These changes are detailed in Table 2.

As demonstrated in Table 2, ALP levels showed an early surge within the first eight weeks after surgery ($p < 0.001$), consistent with the initial osteoblastic differentiation and matrix deposition phase. Osteocalcin levels, however, rose more gradually and continued to increase up to 12 weeks ($p < 0.001$), indicating ongoing mineralization and remodeling activity. Radiographic assessments revealed progressive fracture healing, with callus formation visible at 4 weeks and cortical bridging at 8 weeks. At 12 weeks, 132 patients (88%) achieved complete union, while 15 patients (10%) demonstrated delayed healing, and 3 patients (2%) developed non-union. The correlation between biochemical markers and radiological union was examined using the Radiographic Union Scale for Tibial fractures (RUST) scoring system. Both serum ALP and osteocalcin showed significant positive correlations with RUST scores. As summarized in Table 3, osteocalcin demonstrated a stronger correlation ($r = 0.72$, $p < 0.001$) compared to ALP ($r = 0.66$, $p < 0.01$), emphasizing its superior predictive value for bone healing.

As shown in Table 3, patients with higher osteocalcin levels exhibited faster radiographic union and higher RUST scores at 12 weeks. This correlation confirms osteocalcin's role as a sensitive late marker of osteoblastic activity and bone maturation.

The healing outcomes were further stratified by biochemical marker levels. Table 4 presents a comparison of mean ALP and osteocalcin concentrations across different healing statuses. Patients who achieved early union (≤ 12 weeks) had significantly higher levels of both biomarkers compared to those with delayed healing or non-union ($p < 0.05$).

Table 4 demonstrates that both ALP and osteocalcin levels were markedly lower in delayed and non-union cases, confirming their diagnostic utility as early indicators of impaired bone healing.

Patients with early union exhibited a peak rise in ALP by 8 weeks, followed by sustained osteocalcin elevation through the 12-week period, paralleling the biological sequence of matrix formation and mineralization.

In summary, the results clearly demonstrate that serum alkaline phosphatase and osteocalcin levels increase significantly during bone healing following internal fixation of long bone fractures, and these elevations are strongly correlated with radiographic union scores. Osteocalcin, in particular, showed a higher degree of sensitivity and predictive value for assessing fracture consolidation, indicating its importance as a reliable biochemical marker for monitoring bone healing progress in orthopedic practice.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Parameter	Value (n = 150)
Mean Age (years)	38.2 ± 11.6
Gender (Male/Female)	102 / 48
Fracture Site	Femur 46%, Tibia 38%, Humerus 16%
Etiology	RTA 62%, Fall 28%, Others 10%
Type of Fixation	Plate fixation 58%, Intramedullary nail 42%
Diabetes Mellitus	21 (14%)
Smokers	31 (20.7%)

Table 2: Serial Changes in Serum ALP and Osteocalcin Levels at Different Postoperative Intervals

Time Interval	ALP (IU/L) Mean ± SD	Osteocalcin (ng/mL) Mean ± SD
Preoperative	82.4 ± 13.9	14.8 ± 5.1
4 weeks	104.6 ± 16.2	19.6 ± 6.2
8 weeks	129.7 ± 18.8	24.3 ± 6.9
12 weeks	122.5 ± 17.5	28.7 ± 7.1

Table 3: Correlation Between Biochemical Markers and Radiographic Healing (RUST Scores)

Parameter	Correlation with RUST Score	p-value
Serum ALP	r = 0.66	< 0.01
Serum Osteocalcin	r = 0.72	< 0.001

Table 4: Comparison of Mean ALP and Osteocalcin Levels Across Healing Outcomes

Healing Status	n (%)	Mean ALP (IU/L)	Mean OC (ng/mL)
Early Union (≤ 12 weeks)	132 (88%)	126.8 ± 19.3	30.1 ± 6.8
Delayed Healing (> 12 weeks)	15 (10%)	104.2 ± 18.7	22.4 ± 5.9
Non-Union	3 (2%)	96.5 ± 16.2	18.6 ± 5.3

DISCUSSION

The present study investigated the relationship between serum biochemical markers alkaline phosphatase (ALP) and osteocalcin (OC) and radiological bone healing after internal fixation of long bone fractures[10]. The results demonstrated a significant rise in both ALP and OC during the postoperative period, with ALP peaking around the eighth week and osteocalcin showing a sustained increase through the twelfth week. Both markers correlated strongly with radiographic union scores, confirming their role as sensitive indicators of osteoblastic activity and bone remodeling[11].

Bone healing after internal fixation is a highly regulated biological process characterized by osteogenic cell proliferation, matrix formation, mineralization, and remodeling. In the early stages, osteoblasts secrete matrix vesicles rich in ALP, which hydrolyzes organic phosphate esters, increasing the local phosphate concentration necessary for hydroxyapatite crystal formation[12]. This mechanism explains the early postoperative rise in serum ALP levels observed in the present study. Similar findings were reported by Wu et al. (2021) and Neve et al. (2021), who observed maximal ALP activity within the first 6–8 weeks following fracture fixation, correlating with the onset of mineralized callus formation[13,14].

In contrast, osteocalcin is synthesized by mature osteoblasts during later stages of bone healing and serves as a marker of bone matrix maturation. The continuous increase in osteocalcin levels up to the twelfth week in this study aligns with the ongoing bone remodeling phase, where newly formed callus tissue gradually transforms into lamellar bone. Previous investigations by Kranioti et al. (2020) and Wiktor et al. (2022) support this pattern, emphasizing that osteocalcin reflects sustained osteoblastic function during the later stages of healing[15,16].

The strong positive correlation observed between osteocalcin and the Radiographic Union Scale for Tibial fractures (RUST) scores ($r = 0.72$, $p < 0.001$) suggests that osteocalcin is a particularly sensitive predictor of fracture consolidation. Patients exhibiting higher OC levels had faster and more complete radiographic union, while those with delayed healing or non-union had persistently lower levels of both markers. These findings are in agreement with Sharif et al. (2019) and Al-Khateeb et al. (2020), who also demonstrated that reduced osteocalcin levels were associated with impaired osteogenesis and delayed union[17,18].

The temporal relationship between ALP and OC changes provides further insight into the biological sequence of bone repair. The early surge of ALP activity reflects initial matrix deposition, while the gradual and prolonged rise in osteocalcin signifies continued mineralization and remodeling. Monitoring both markers together offers a comprehensive view of bone regeneration dynamics, particularly in the postoperative setting where early detection of delayed healing is crucial[19,20].

Another key aspect highlighted in this study is the clinical utility of biochemical monitoring. Radiographs, though essential, often lag behind actual biological events and may underestimate early bone repair. In contrast, biochemical markers provide a quantitative and earlier reflection of osteoblastic activity, allowing clinicians to identify patients at risk of delayed healing before structural complications occur. Moreover, such markers can be easily measured through simple blood tests, making them cost-effective and widely applicable in routine orthopedic follow-up[21,22].

However, the study has some limitations. Being a single-country, dual-center study, variations in patient nutrition, comorbidities, and implant types might influence biochemical profiles. Additionally, factors such as vitamin D deficiency or concurrent systemic inflammation may affect ALP or osteocalcin values independently of bone healing. Future studies with larger multi-institutional cohorts, longer follow-up periods, and inclusion of additional markers such as bone-specific ALP and procollagen type 1 N-terminal propeptide (P1NP) could provide a more comprehensive understanding[23,24].

Overall, the findings of the present study reinforce the concept that bone turnover markers can serve as reliable adjuncts to radiographic evaluation. Their combined use not only aids in assessing the biological progression of fracture repair but also facilitates individualized patient management by identifying delayed union at an early stage, optimizing rehabilitation timing, and reducing unnecessary radiographic exposure[25].

CONCLUSION

This study concludes that serum alkaline phosphatase and osteocalcin are reliable biochemical indicators of bone healing following internal fixation of long bone fractures. The progressive rise in ALP reflects early osteoblastic activity and mineralization, whereas osteocalcin represents the later stages of matrix maturation and bone remodeling. Both markers demonstrated strong correlations with radiographic union scores, with osteocalcin showing superior predictive accuracy. Routine monitoring of these biochemical markers in postoperative patients provides a simple, non-invasive, and cost-effective means to evaluate the biological progress of bone healing. Incorporating ALP and osteocalcin testing into standard follow-up protocols can aid in early detection of delayed or non-union, improve clinical decision-making, and enhance patient outcomes in orthopedic practice. In summary, serial measurement of ALP and osteocalcin should be considered as a valuable adjunct to radiological assessment in the management and monitoring of fracture healing after internal fixation of long bones.

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Authors' Contributions:
M.Q.F. – Concept and study design, manuscript drafting, and supervision.
S.H.A. – Data collection, biochemical analysis, and interpretation.
H.R.H. – Radiological evaluation and correlation analysis.
P.A. – Statistical data analysis and tabulation.
F.H. – Literature review and manuscript editing.
M.Y.M. – Final review, critical revision, and approval of the manuscript.
All authors have read and approved the final version of the manuscript for submission.

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