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Evaluation of serum bone specific alkaline phosphatase levels in isolated closed diaphyseal fractures of long bones in relation to fracture healing

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Abstract

Introduction: In day-to-day practice, progression of bone healing is assessed mainly by clinico-radiological parameters. Furthermore, clinicians are unable to identify the delayed and non-unions early, and even advanced imaging techniques may not be helpful in these cases. To date, the methods used to monitor the bone healing process have been based on the patients' assessment and the radiographic findings. In view of the fact that patient opinion is highly subjective, that the radiographic findings depend on the radiologist's experience and that the monitoring of bone healing is a long-lasting process, measurements of biochemical parameters appear to be the only objective evidence of the changes occurring during bone regeneration. The aim of this study was to examine whether the assessment of Serum bone specific ALP (BsALP) as a biochemical parameter in the early posttraumatic phase may indicate the course of fracture healing.

Methods: Changes in BsALP levels were observed at definitive intervals in 30 adult patients (enrolled as per inclusion/exclusion criterion) with closed fresh (within 1 week) traumatic diaphyseal fractures of long bone. All the patients had been surgically treated. Regular follow up of these patients was done till 6 months. The changes in serum BsALP levels were recorded and correlated with the clinico-radiological progression of fracture healing in these patients.

Result: The mean BsALP increased significantly from baseline to 6 and 12 weeks and then decreased significantly at 16 to 24 weeks.

Conclusion: BsALP levels were increased in all cases of closed isolated long bone diaphyseal fractures with maximum increase at 12 weeks and never reached to baseline levels till 24 weeks. The increase in BsALP levels was more in surgical fixation done with nailing as compared to plating. No relationship was observed between BsALP levels and fracture healing outcome.

Keywords: Serum BsALP, delayed union and non-union

Introduction

Fracture healing is a proliferative physiological process to facilitate the repair of a fracture ^[1]. This is a continuous physiological process to achieve union. This process of fracture union is characterized by the production of a new organic matrix, known as osteoid and its subsequent mineralization, thus bridging the gap between two bony fragments by bridging callus. This fracture healing process should be serially quantifiable / measureable ^[2].

Till date, there is no clinically validated method to measure healing progression. So a valid method for bone union is desired to measure the progress of union. Thus, the values yielded by measurement should be on a continuous numerical scale ^[3]. However till now, clinicians watch for an end point of complete union without bothering for documenting the values signifying progress of healing ^[4].

Bone-formation markers are indicative of osteoblastic activity. Although type-III collagen, a non-osteoblastic protein, is the initial collagen laid down during the healing of fractures, it is replaced by type-I collagen when bone formation begins. More specific measures of osteoblastic activity include osteocalcin, the major non-collagenous protein of bone matrix, and the isoenzyme bone-specific alkaline phosphatase (BsALP) ^[5].

Laurer *et al.* studied the increase in BsALP activity in relation to the type of trauma and have concluded that the initial decrease in the activity of BsALP is not just a consequence of the

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bone's response to the trauma, but also a total stress response connected to the injury and the surgery. The post-trauma increase in the BsALP activity is connected to the localization of the fracture and it increases parallel to the applied osteosynthesis. A large increase of the quantity of callus formation is present in some patients, followed by an outstanding increase of activity of total ALP in addition to the bone isoenzymes [14].

Muljacić *et al.* examined whether the assessment of BsALP as a biochemical parameter in the early post-traumatic phase may indicate the course of fracture healing. They assessed the activity of BsALP in the serum of 41 patients who sustained long bone fractures. treated surgically were followed up radiologically for several months. They concluded that monitoring changes in the biochemical parameters ALP and BsALP allows early detection of fracture healing rates. A minor increase in the activity or no change in the level of the biochemical parameters ALP and BsALP in the period of the first two weeks indicates successful fracture fixation, rapid bone healing and the formation of a minimal or insignificant callus. It was also concluded that a major increase in the activity of the biochemical parameters such as ALP and BsALP in the period of the first two weeks indicated inadequate fracture fixation, delayed bone healing and the formation of a visible and significant callus [6].

Alkaline phosphatase (ALP) is a homodimeric metallo enzyme responsible for removing phosphate group from nucleotides, proteins, and alkaloids. As the name suggests, alkaline phosphatases are most effective in an alkaline environment. ALP is found in many tissues including bone, liver, intestine, kidney, placenta and germ cell. ALP originates primarily from liver and bone, bone isoenzyme is the marker of bone formation and is found in osteoblast. BsALP is increased in metabolic bone disorders like osteoporosis, osteomalacia and rickets [5].

As BsALP levels suggest the bone forming activity responsible for both bone matrix formation and its mineralization. This study was carried out to correlate serial BsALP levels with progression of fracture healing process which might predict the fracture healing outcome earlier and may allow to intervene earlier.

Materials and Method

The study was carried out in the Department of Orthopaedics at Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun. The study included 33 patients over a period of 12 months. Subject were recruited from patients presenting to OPD/Emergency with isolated diaphyseal fracture after obtaining written informed consent and approval of institutional ethical committee. Patients included in the study were those of age group 18-45 years with isolated closed diaphyseal fractures of long bones presenting within 1

week. Patients with metabolic bone disease, Chronic kidney disease, Chronic liver disease, malignancy, pregnancy, polytrauma, segmental fractures Immunocompromised patients, patients on immunosuppressant drugs, and pathological fractures were excluded.

Baseline BsALP levels were done by Ostease method on Access-2 in the NABL accredited lab and fracture pattern of the patients were recorded. Follow-up were done at 6, 12, 16, 24 weeks and patients were examined clinically, radiologically and biochemically (BsALP). Clinically gentle examination of fracture side for swelling, mobility, tenderness and ability to bear weight were done. Radiologically the fracture union was defined as the time when three out of four cortices were formed. An antero-posterior and lateral radiograph of the affected limb were done.

Result

The study population consisted of 27 (81.8%) males and 6 (18.2%) females with majority in the age group of 18-25 years (54.5%) followed by 36-45 years (24.2%) and 26-35 years (21.2%) age groups. Majority of the injuries were reported to be due to the road traffic accidents with lower limb fracture among majority (57.6%) of the patients.

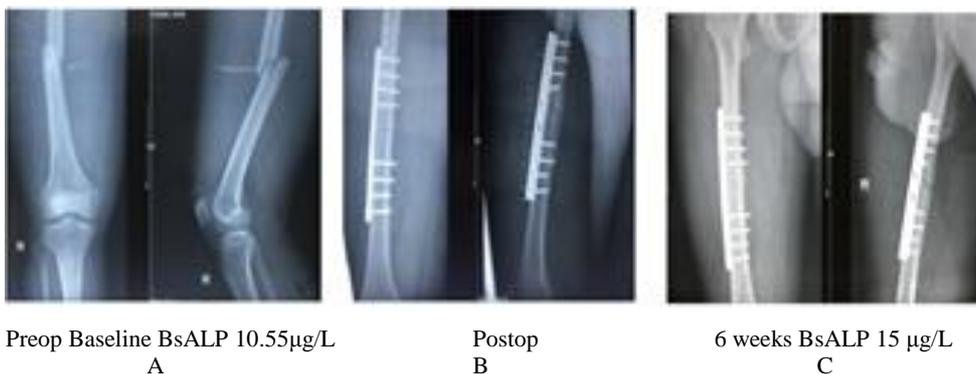
The mean BsALP increased significantly from baseline to 6 and 12 weeks and then decreased significantly at 16 to 24 weeks. There was a mean percentage increase of 28.84% in BsALP from baseline to 6 weeks, 45.09% increase at 12 weeks, 40.73% increase at 16 weeks and 29.35% increase at 24 weeks. The BsALP reached its peak at 12 weeks which was followed by a decrease of 7.95% at 16 weeks and 28.67% at 24 weeks. However the levels of BsALP never reached baseline till last follow up.

There was a significantly higher percentage increase of BsALP from baseline to 6, 12, 16 and 24 weeks among nailing group in comparison to plating group. There was a significantly higher percentage increase of BsALP from baseline to 6 weeks and 12 weeks among Non-union group in comparison to Union and Delayed union groups.

Table 1: Statistical analysis of BsALP levels of all patient at different intervals.

	Bs ALP				
	Baseline	6 weeks	12 weeks	16 weeks	24 weeks
Mean	16.56	23.27	30.16	27.94	23.44
Median	12.73	19.40	26.80	26.00	20.59
Std. Deviation	12.82	11.95	12.77	11.37	11.71
Minimum	5.75	10.00	10.50	12.20	9.00
Maximum	67.30	62.96	68.00	62.00	60.00
Range	61.55	52.96	57.50	49.80	51.00

Case 1



Preop Baseline BsALP 10.55µg/L
A

Postop
B

6 weeks BsALP 15 µg/L
C

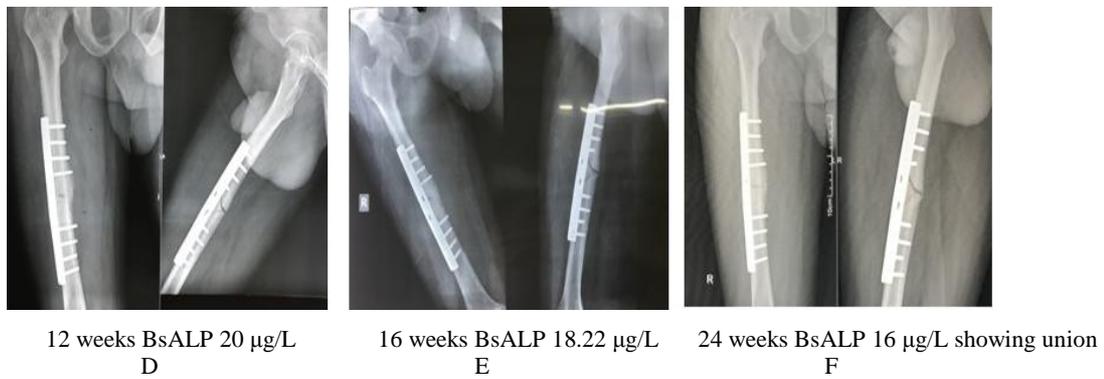


Fig 1: BsALP levels at different intervals in dphyseal # of femur fixed with DCP

Discussion

Bone turnover markers are routinely used in the diagnosis or treatment monitoring of several bone diseases such as osteoporosis or Paget’s disease and shown to correlate with clinical findings and bone imaging. In addition they have also been studied for monitoring the healing process of fractures and for the early detection of fracture-healing disturbance (7). Bone turnover markers level vary during the course of

fracture repair with their rates of change being dependent on the size of the fracture and the time that it will take to heal. Thus early knowledge of the individual progress of fracture could help to keep off delayed or non-union by enabling modification of the host’s biological response (2).

Case 2

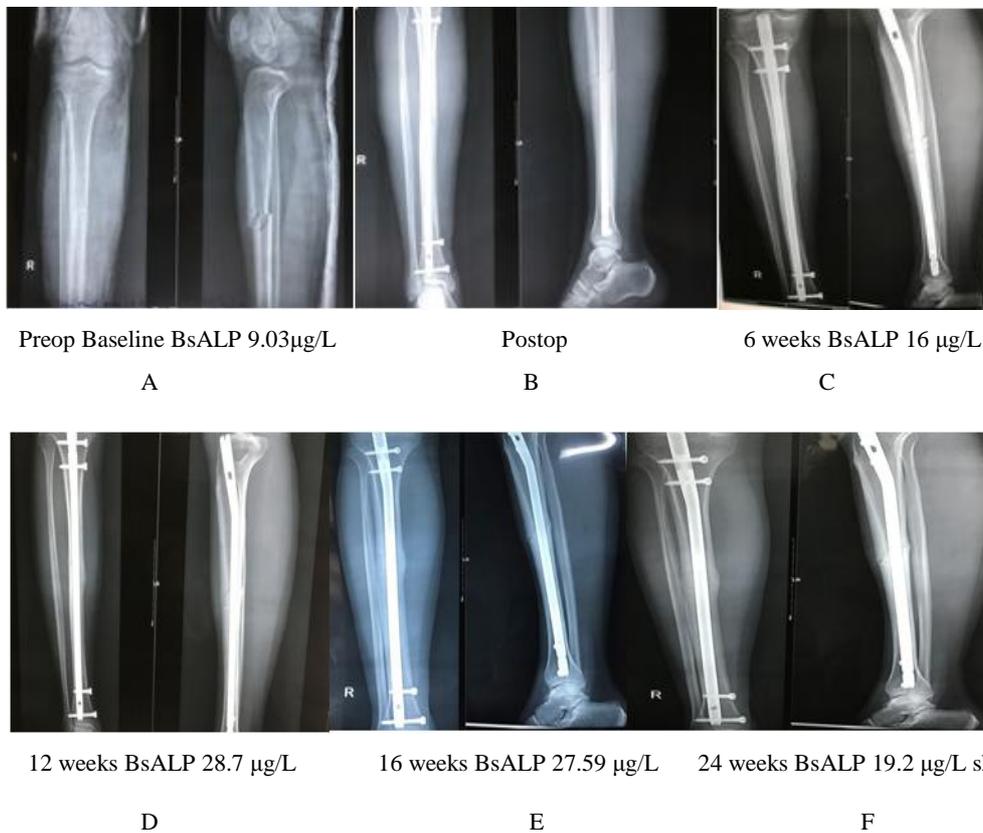


Fig 2: BsALP levels at different intervals in dphyseal # of tibia fixed with IMILN

In our study, non union was seen in 2 patients and delayed bone fracture healing was also seen among 2 patients. The similar findings were also observed in the study done by Stoffel *et al.* in which, delayed bone fracture healing was observed in 2 cases with high energy trauma [2].

In our study, the mean Bone Specific ALP increased significantly from baseline to 6 weeks and 12 weeks and then decreased at 16 weeks and 24 weeks. Similarly, there was a maximum increase in levels of BsALP between 8 and 12 weeks in the study done by Leung *et al.* who measured the levels of BsALP in 49 patients of closed fractures of long bones [7].

In the current study, there was a mean percentage increase of 28.84% in serum BsALP from baseline to 6 weeks, 45.09% increase at 12 weeks. The serum alkaline phosphatase reached its peak at 12 weeks which was followed by a decrease of 7.95% at 16 weeks and 28.67% decrease at 24 weeks. Although BsALP levels had not reached to baseline levels. Ingles *et al.* studied 20 patients with fracture distal Tibia and Fibula and followed BMTs for 52 weeks and found that all BTMs except BsALP were still elevated at 52 weeks while BsALP returned to base line [8]. The levels of BsALP in our study had not reached to baseline levels because in our study patients were followed only upto 24 weeks.

In our study, there was statistically no significant difference in the levels of BsALP on inter group comparison of union v/s non union at baseline, 6 week, 12 weeks, 16 week and 24 weeks. It was also observed there was statistically no significant difference in the levels of BsALP on inter group comparison of delayed union v/s union and delayed union v/s non union at baseline, 6 week, 12 weeks and 16 weeks. However, there was statistically significant difference in the levels of BsALP on inter group comparison of delayed union v/s union and delayed v/s non union at 24 week. However this is not helpful in performing early intervention procedures in delayed healing cases. So as per our study BsALP is not a useful indicator to detect non union at early stage and to do early intervention.

In contrast to our study, S. Ajai *et al.* [2] concluded that serum ALP levels are useful indicator in predicting the fate of fracture healing. They studied 95 patients of simple diaphyseal fracture in adult patients for 9 months, out of which 18 patients went into delayed union and 8 patients went into non union. Similarly S Das *et al.* [9] also studied biochemical markers in 100 patients of long bone fractures out of which 20 patients went into non union and they have concluded that these biochemical markers can be used as adjunct to clinical and radiological evidence of healing.

However, our study is not in concordance with these studies probably because our sample size was small and only 4 patients went into delayed and non union. In addition, our follow up was of shorter duration in comparison to these studies. These might be the reasons that we were not able to establish statistically significant correlation between fracture healing and BsALP levels.

In our study, values of BsALP showed higher percentage increase of BsALP from baseline to 6, 12, 16 and 24 weeks among Nailing group in comparison to plating group. Mulijacic *et al.* concluded that patients treated by the conservative method have had the largest increase in ALP after the injury, while the smallest increase was reported with patients who had been treated by stable osteosynthesis. It can be assumed that serum ALP activity depends on the stability of the bone fragments after the bone fracture [6].

Conclusion

In the light of these results we can conclude that:

1. BsALP increases in all cases of closed isolated long bone diaphyseal fractures.
2. The maximum increase in its level occurs at 12 weeks.
3. The levels of BsALP never reached to baseline till last follow ups.
4. The increase in BsAlp levels is more in surgical fixation done with nailing as compared to plating.
5. There is no relationship between BsALP levels and fracture healing outcome. Study on large sample size with longer followup are required to establish relationship between fracture healing out come and level of BsALP.

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