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Original Scientific Article

The Changes of Bone-Specific Alkaline Phosphatase (BsALP) Associated With Callus Formation and Rate of Bone Healing

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Abstract. The aim of this study was to examine whether the volume of bone-specific alkaline phosphatase (BsALP) as a biochemical parameter in the early posttraumatic phase may indicate the speed of fracture healing. The evaluation of the bone healing process has been based on the patient's subjective statement and radiographic findings. The activity of bone-specific alkaline phosphatase has been measured in the sera of 41 patients who have been diagnosed with fractures of long bones. All the patients have been surgically treated. The activity of BsALP was measured on each seventh day during a four-week period. On the same patients the radiologically follow-up tests have been made during a period of seven months. Our research has shown that the increase of alkaline phosphatase correlates with an increase of BsALP levels. The volume of callus correlates with the level of ALP and BsALP. The result leads us to a conclusion that by monitoring the changes of biochemical parameters: alkaline phosphatase and bone-specific alcaline phosphatase, we can be able to predict the dynamics of the bone healing.

Keywords: Prognostic Significance, BsALP, Long Bone Fractures

INTRODUCTION

Bone fracture healing is a complex biological process. Experimental studies show that the levels of bone-specific alkaline phosphatase (BsALP) in the osteoblastline cells and bones are proportional to the formation of collagen.[1,2] Clinical studies also show that the level of BsALP in the serum correlates with the bone formation rate.[3,4]

Various authors have shown that regardless of the treatment method (conservative or surgical, or even compressive osteosynthesis) the maximum values of the total ALP occur after the twenty-first day after the injury.[5,6] Statistical analysis and the method of correlation have proved a significant correlation in the changes of the value of bone isoenzymes in relation to the changes of the total ALP, at the level of 1.1 % already on the seventh day after the injury.[5] 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. Based on these findings, it can be assumed that ALP activity depends on the stability of the bone fragments after the bone fracture. This has been confirmed by other studies which prove that unstable osteosynthesis results with greater mobility to bone fragments in comparison to the stable osteosynthesis, while conservative treatment methods provide the greatest mobility to bone fragments.[7–9] Laurer *et al.* have 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 bone's response to the trauma, but also a total stress response connected to the injury and the surgery.[10] The posterior increase in 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 isoenyzmes.

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Such increased values of these parameters are present solely in patients with the long bones fractures, combined with traumatic injuries of the brain.[11,12]

A continual increase in biochemical levels is noticed with these patients from the first until the twenty-first day after the injury, which corresponds to the increase noticed in patients without traumatic brain injuries.[5,13,14]

The upcoming of heterotrophic ossification cannot be prevented by corticosteroids.[15,16] Studies carried out by Bowles. *et al.* do not show a continuous increase of the total ALP nor the BsALP between the first day and the tenth week after the injury.[17] Their measurements show that the values of total ALP and BsALP significantly decrease until the fourth day after the injury, on the eighth day they return to the values of the first day, and then consequently continually increase until the tenth week. By their subsequent studies carried out on tibial fractures, Bowles *et al.* also have found a decrease of ALP in the first week after the injury, whereas in the second week its values begin to increase.[18] These results differ from those of Leung *et al.* , who, by measuring BsALP on 49 adult patients with long bone fractures, have not found the initial decrease in the levels.[19] Researching the total ALP on tibial fractures, Oni *et al.* have not noticed an initial decrease of the levels, while the initial increase of ALP was insignificant.[20]

The increase in the alkaline phosphatase activity in stable osteosynthesis can indicate very early (much earlier than it can be detected by X-ray tests) if the sugery has not been carried out stably enough. The increase in the BsALP activity is reliable proof of all the changes of alkaline phosphatase which occur in the case of bone fractures. Statistical analysis of the changes in alkaline phosphatase and its bone-specific isoenzyme have shown, by the method of correlation, a significant correlation between these two parameters. The possibility of qualitative and quantative separation of alkaline phosphatase isoenzymes shows which group of isoenzymes is responsible for the increase in alkaline phosphatase activity in the serum or the plasma. The aim of this study is to determine the clinical importance of measurement of the bone isoenzymes value in order to estimate the progress of bone healing of the surgically treated fractures.

MATERIAL AND METHODS

Clinical sample

The activity of bone-specific alkaline phosphatase (BsALP) was measured in the sera of 41 patients with long bone fractures. Out of the 41 studied patients, 26 were male, and 15 were female, aged between 15 and 80 years. Following the anamnesis, the patients have undergone laboratory tests (complete blood analysis, total bilirubin, AST, ALT, GGT, sedimentation and urine analysis) and based on the above it has been concluded that their results are within the normal range and are appropriate for our research. We would like to emphasize that in this scientific research, laboratory hematology results were used in addition to X-ray images which were solely done as a part of a regular clinical procedure during the patients' stay at the Clinic and during the routine tests in check-ups after their discharge from hospital. All of the patients had undergone surgical treatment. The BsALP activity was measured in the sera of the patients each seventh day during the period of four weeks.

The examinee group consisted of 100 healthy adults (70 males and 30 females) aged between 25 and 60. From the sera, the level of BsALP was also measured using the same procedure as in the main group. It must be noted that all of the tested from the control group have been informed with the purpose of the testing and voluntarily consented to it.

Laboratory Measurements

The laboratory analysis consisted of two different methods: the method of determining alkaline phosphatase according to Da Foncesca-Wolheim and the method of determining BsALP activity described by S.B. Rosalki and A.Y. Foo in 1984.[21,22]

Radiological Measurements

From the each patient's X-ray result taken on the day of the fracture, the first step was to measure the size of the bone fracture fissure, and then, after the bone was completely healed, the volume of periosteal callus was calculated by mathematical methods.

Statistical Analyses

Quantitative data of the groups were compared using the Mann-Whitney U test, whereas the Friedman test compared the data within various time periods and the Wilcoxon Z test compared two periods. The values $p \leq 0.05$ were considered to be statistically significant[23,24]. All calculations were performed using Statistica 8 Statistical Software.

RESULTS

Parameters according to the fracture type (T – tibia , F – femur,) and the total for the variable of time in days following the injury (first day – 1D, seventh day – 7D, fourteenth day – 14D and the twenty-first day – 21D) and the levels of the BsALP variable (BsALP) were analysed.

All the (33) patients came to the 7th day checking, 9 patients came to the 14th day checking, and to the 21st day checking came only 5 patients. It is evident that in the group T, the average value of the variable BsALP on the twenty-first day is significantly higher than on the first, seventh and fourteenth day, *i.e.* the BsALP level measured on the fourteenth day is significantly higher compared to the first and seventh day, while the BsALP on the seventh day in relation to the first day is significantly lower. In the group F the average level of the BsALP variable is significantly higher on the twenty-first day compared to the first, seventh and fourteenth days, *i.e.* BsALP on the fourteenth day is significantly higher compared to the first and seventh days, while BsALP on the seventh day is much lower compared to the first day (Table 1).

A day to day graph of median BsALP for the group which has had tibia or femoral surgery can be found on the Figure 1.

The variables on the distribution normality have been tested in the group by the Kolomogrov-Smirnov tests. Because all the variables have shown a deviation from the normal distribution, the non-parametrical methods for testing the differences between the variables, have been used.

The differences between the two groups of the surgically treated patients, have been made by the Mann-Witney test. No statistically significant differences have been found between the two groups (tibia-femor) in D1 BsALP P = 0.062; D7 BsALP P = 0.206 and D14 BsALP P = 0.117.

The differences between the days (1, 7, 14, 21) have been tested in the tibia group by the Friedman test. No statistically significant difference has been found between the days (1, 7, 14, 21) in the variable BsALP P = 0.069.

The difference between the each particular day has been tested by the Wilcoxon Signed Ranks Test.The statistically significant differences in the tibia group have been found between day 7 and day 1 in BsALP – P = 0.035; day 14 and day 7 P = 0.028; day 21 and day 7 P = 0.678; day 21 and day 1 P = 0.345; day 21 and day 14 P = 0.225.

The parameters according to the type of fracture and the total value of callus volume (cm^3) are shown in Table 2. It must be noted that the callus volume of 10 cm^3 was taken as the average value of the measured callus volumes. All the values of the callus from 5 to 10 cm^3 are considered small, the values between 0–5 cm^3 are insignificant and the values from 0 cm^3 mean that there is no is callus. The value of the volume of callus between 10 cm^3 and 15 cm^3 are significant, and the values of 15 cm^3 and more are of especial significance. From the table, it can be seen that the average value of the volume of the callus is much lower in Group T in comparison to Group F.

Table 1. Parametres according to fracture type and median value for the variables D1 BsALP, D7 BsALP, D14 BsALP and D21 BsALP

Group		D1 BsALP	D7 BsALP	D14 BsALP	D21 BsALP
Tibia	N	33	33	9	5
	Median	27.00	13.00	53.00	64.00
	Q1	11.00	8.00	23.00	52.00
	Q3	37.00	28.00	65.00	108.00
	Interquart. range	26.00	20.00	42.00	56.00
	Min.	2.00	2.00	14.00	30.00
	Max.	368.00	253.00	148.00	278.00
	Range	366.00	251.00	134.00	248.00
Femur	N	7	7	1	
	Median	58.00	23.00	2.00	–
	Q1	23.00	11.00	2.00	–
	Q3	73.00	68.00	2.00	–
	Interquart. range	50.00	57.00	0.00	–
	Min.	6.00	5.00	2.00	–
	Max.	126.00	178.00	2.00	–
	Range	120.00	173.00	0.00	–

Q1 – 1. quartila (25 percentila); Q3 – 3. quartila (75 percentila); N – Number of examinee; Min – minimal value; Max – maximal value

The parameters according to the decrease, without change and the increase in the value of BsALP, according to days and the difference of BsALP according to days, and the volume of the callus are shown in Table 3. It can be concluded that the decrease of the value of BsALP according to days, as well as the insignificant changes in the value of BsALP according to the days of testing, result in the average formation of a small callus volume of 7.98 cm^3 and 7.11 cm^3, and that the increase in the value of BsALP according to days corresponds to the formation of the mean significant volume of callus of 35.81 cm^3.

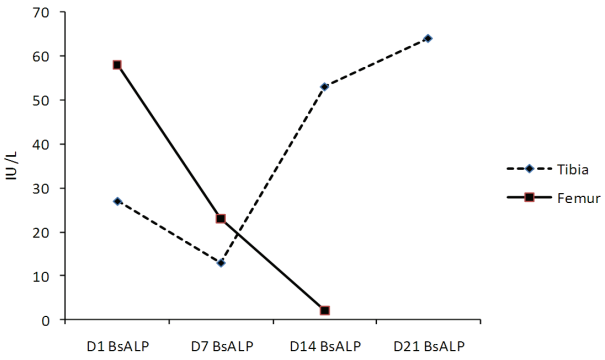

Figure 1. A day to day presentation of BsALP medians for the examinees who have had tibia or femur surgery.

Table 2. The parameters according to the type of fracture and the total value of callus volume (cm^3)

Group		D1 BsALP
Tibia	N	33
	Median	27.00
	Q1	11.00
	Q3	37.00
	Interquartile range	26.00
	Min.	2.00
	Max.	368.00
	Range	366.00
Femur	N	7
	Median	58.00
	Q1	23.00
	Q3	73.00
	Interquartile range	50.00
	Min.	6.00
	Max.	126.00
	Range	120.00

Q1 – 1. quartila (25 percentila); Q3 – 3. quartila (75 percentila); N – Number of examinee; Min – minimal value; Max – maximal value.

DISCUSSION

There is some evidence, in contemporary literature, which shows that by measuring the activities of the total alkaline phosphatase, it is possible to estimate the rate of the bone formation, except in cases of liver disease.[25] Research has shown that an increase of alkaline phosphatase level is followed by an increase of the value of the BsALP level. In adults, half of the activity of the total alkaline phosphastase consists of BsALP and the other half of liver isoenzymes.[25,26] Therefore, by measuring the bone esoenzymes, we have better insight into the dynamics of bone turnover, the growth and the healing of the bones.[27]

Although a lot has been achieved, our research is the first attempt to analyze the BsALP and link it to the bone formation and healing. Results of our study show that the volume of callus is followed by a decrease of value and an increase of bone isoenzymes value.

Although our research has shown connection between the bone isoenzymes and the callus volume on the seventh, fourteenth and twenty-first day, this connection is statistically significant only on the seventh day. These results are related to the group of tibia and the femoral fracture group. For the groups with single femoral fracture and single tibia fracture, no statistically significant connection between the callus volume and the bone isoenzmyes has been proved in a single measuring day, which can be explained by a rather small sample used in this research. The research results of Laurer *et al.* show a bone isoenzymes increase from the very first day and statistically significant increase from the seventh day after the fracture, but only in cases of long bone fractures.[10] The increase of the bone isoenyzmes immediately after the fracture was measured by Leung *et al.* while research carried out by some authors shows a decrease in the activity of bone isoenzymes in isolated fractures of tibia from fourth to eight day after the fracture.[17,18,19] Similar results were shown by Bowles *et al*.[17,18] Bowles *et al.* consider this initial decrease to be the effect of the system's inflammatory response to trauma. It is known that cytokines, which release various inflammatory cells postraumatically activated, may initially directly decrease bone isoenzyme activity or by activating the prostaglandin process.[22] It is also known that interleukin 1 (Il-I) first of all causes bone resorption and leads to the reduction of the markers specific for bone formation. Continuing the process caused by trauma, simulation, replication and the proliferation of the osteoblast take place, which is essential for bone healing.[28] Different results of the aforementioned author can be explained by complexity of factors which affect the ALP and BsALP levels in blood. These include the influence of the daily rhythm of bone turnover, the influence of the seasons, age, sex and ethnicity. The maximum value of bone isoenzymes in blood is found during puberty. Bone turnover is more intense when menopausal and postmenopausal women are concerned, than in case when women are in their reproductive age and it is greater when men of the same age are concerned. In men, the concentration of the indicators of bone turnover is greater than in women until the menopause. A greater concentration of the value of the indicators of bone turnover is noticed in men aged between 20 and 30 and from 50 to 60 years. Ethnic differences in the particularities in the bone metabolism are manifested within the decreased values with members of the black race. A higher concentration of daily oscillations of biochemical parameters of bone turnover are noticed from 2 a.m. to 8 a.m. and lower concentrations between 1 p.m. and 11 p.m. Increased physical activity can also lead to a change of 15–40 % of) biochemical indicators of the bone turnover in a period between 24 and 72 hours after physical strain. Professional sportsmen have a value factor of bone turnover which differs to that of the rest of the population.[29,30]

Considering the stated factors and significant biological variations of biochemical indicators of bone turnover, various results of research in this area can be explained, and there is a need for careful observation of the causes related to the conditions and time of the monitoring of the individual examenees. In this way, it

Table 3. The parameters according to the decrease. without change and the increase in the value of BsALP, according to days and the difference of BsALP according to days, and the volume of the callus

BsALP level		D1 BsALP	D7 BsALP	D14 BsALP	Difference BsALP on D7 and D1	Difference BsALP on D14 and D1	Callus volume (cm^3)
Decrease	N	15	15	3	15	3	15
	Median	45.00	16.00	32.00	–34.00	–69.00	0.00
	Q1	28.00	9.00	2.00	–51.00	–194.00	0.00
	Q3	73.00	35.00	148	–16.00	–29.00	9.05
	Interquartile range	45.00	26.00	146.00	35.00	165.00	9.05
	Min.	9.00	2.00	2.00	–294.00	–194.00	0.00
	Max.	368.00	128.00	148.00	–6.00	–29.00	80.42
	Range	359.00	126.00	146.00	288.00	165.00	80.42
No change	N	16	16	2	16	2	16
	Median	11.50	11.50	38.00	–1.00	13.50	3.99
	Q1	8.00	5.00	19.00	–7.50	6.00	1.63
	Q3	22.5	22.5	57	3.50	21.00	9.52
	Interquartile range	14.50	17.50	38.00	11.00	15.00	7.89
	Min.	2.00	3.00	19.00	–23.00	6.00	0.00
	Max.	37.00	29.00	57.00	21.00	21.00	29.06
	Range	35.00	26.00	38.00	44.00	15.00	29.06
Increase	N	9	9	5	9	5	9
	Median	34.00	54.00	53.00	20.00	19.00	25.56
	Q1	27.00	17.00	23.00	4.00	–5.00	13.62
	Q3	41.00	68.00	65.00	23.00	38.00	44.77
	Interquartile range	14.00	51.00	42.00	19.00	43.00	31.15
	Min.	4.00	2.00	14.00	–20.00	–8.00	5.50
	Max.	58.00	253.00	75.00	213.00	71.00	113.04
	Range	54.00	251.00	61.00	233.00	79.00	107.54

Q1 – 1. quartila (25 percentila); Q3 – 3. quartila (75 percentila); N – Number of examinee; Min. – minimal value; Max.– maximal value.

would be possible to avoid the unwished effect of factors which increase the variation and consequently conceal the clinical appearance or a change which should be studied, and the results would be more comparable.

The amount of BsALP is proportional to callus size. This is the conclusion of both in vitro and in vivo studies, but only based on comparison. Our research and the measuring of the size of the bone isoenzymes has also confirmed this.[31–33] Bone fracture causes enhanced bone turnover and biochemical indicators of up to 50 %, however the indicators can remain increased during 6–12 months due to cellular activity during the bone healing.[22] Our results have also had a great number of patients with developed increased callus that measured increased bone isoenzymes of up to 50 % in the period between the first and fourteenth day.

The volume of callus formation is proportional to the increase in BsALP activity. By analyzing the amount of callus we have noticed that the increased value shows the prolonged time of bone healing after trauma, while the smaller or radiographically invisible callus is connected to the rapid healing of the fracture. Analysis of the changes in activity of BsALP has shown that the decrease of value on the seventh day compared to the first day, *i.e.* the day of the trauma, is equal to the fall in value on the fourteenth day compared to the first day and is followed by the formation of insignificant callus. BsALP activity analysis on the days when no significant changes in value were noticed, are followed by the formation of a small amount of callus. The increase of the value of BsALP is followed by the formation of a significantly large amount of callus.

As the formation of callus is visible only after an extended period of time, *i.e.* is finally completed after the healing of the bone fracture, the measured BsALP after the first, seventh and fourteenth day, immediately

after the trauma, could in advance indicate the speed at which bone healing will take place. The activity of bone isoenzymes does not only indicate the speed of the future bone healing but at the same time shows how well the operation of the osteosynthesis of the bone fracture has been carried out, which is also very important. It is known that a well performed operation leads to faster healing of the bone and that it is not followed by the formation of callus. In fact, the formation of a larger or a smaller amount of callus is related to the smaller or greater instability of bone fragments which leads to prolonged bone healing.

CONCLUSION

The results of our study can be divided into two groups. The first group of conclusions is related to the dynamics of the early changes in the biochemical parameters of the alkaline phosphastase and the bone isoenzymes after the fracture, and the second group of conclusions is related to the role of the observed early changes as predictors of the speed of the fracture healing.

1) By monitoring the changes of the biochemical parameters of alkaline phostastase and the bone isoenzymes, it is easely possible to detect the dynamics of the healing of the bone fracture early. Changes in the alkaline phosphastase activity are followed by the almost identical changes in the value of the bone isoenzymes. The volume of the formation of the callus is directly proportional to the increase of activity of the stated parameters.
2) A small increase in activity or the absence of changes of the biochemical parameters (alkaline phosphastase and bone coenzymes) up until the fourteenth day is an indicator of the successfully performed osteosynthesis and the rapid healing of the bone fracture with the formation of minimal or insignificant callus. A greater increase in the activity of biochemical parameters (ALP and BsALP) up until the fourteenth day is an indicator of the poorly performed osteosynthesis, the slower healing of the bone fracture with the formation of a visible and significant amount of callus volume.

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SAŽETAK

Utjecaj vrijednosti koštanog koenzima (BsALP) na stvaranje kalusa i brzine koštanog cijeljenja

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Cilj ovog istraživanja bio je utvrditi da li količina BsALP kao biomkemijski parametar u ranom posttraumatskom razdoblju može indicirati brzinu koštanog cijeljenja. Procjena cijeljenja kosti zasnovana je na pacijentovim subjektivnim izjavama , te potvrđena rendgenskim nalazima.Aktivnost specifične koštane alkalne fosfataze izmjerena je na grupi od 41 pacijenta kojima je dijagnosticirana fraktura dugih kostiju. Svi su pacijenti bili tretirani kirurški. Aktivnost BsALP je mjerena svaki sedmi dan u periodu od četri tjedna. Isti pacijenti radiološki su kontrolirani sedam mjeseci. Naša istraživanja su pokazala da je povećanje alkalne fosfataze u korelaciji sa povećanjem razine BsALP. Volumen kalusa korelira sa smanjenjem, i na jednaki način povećanjem razine ALP i BsALP. Rezultati upućuju na zaključak da se promatranjem promjena biokemijskih parametara alkalne fosfataze i specifične koštane alkalne fosfataze može predvidjeti dinamika koštanog cijeljenja.