

## Study of Serum Alkaline Phosphatase Level in Rheumatoid Arthritis

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### ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a chronic progressive multisystem disease primarily causing inflammation of joints with potential of synovial inflammation to cause cartilage damage and bone erosion. It results in painful deformity and immobility especially in fingers, wrists, feet and ankle. Resorption and formation of bone are normally tightly coupled. Changes leading to decreased rates of bone formation or increased rates of bone resorption or both may cause a decrease in bone mass. Bone alkaline phosphatase (BALP) is a metalloprotein that contains Zn<sup>++</sup> and Mg<sup>++</sup>, both of which are necessary for its catalytic function. It is anchored to membrane inositol phosphate on the outer surface of osteoblasts. However, in serum it is found anchorless (soluble form). BAP reflects the biosynthetic activity of these bone forming cells. It has been shown to be sensitive and specific marker of bone metabolism.

**Aims and Objectives:** To estimate the level of Serum Alkaline Phosphatase in study group and to compare it with that of controls.

**Material and Methods:** A case control study was carried out in the Department of Biochemistry in collaboration with the Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India between October 2013 to September 2015. Seventy six cases of RA and 76 age, sex matched healthy individual taken as controls for the study. Serum Alkaline Phosphatase was measured using colorimetric methods.

**Results:** Statistically significant higher levels of Alkaline Phosphatase (cases-216.22 ± 59.96IU/L, controls-164.17 ± 50.67IU/L), were found among cases as compared to controls.

**Conclusion:** The results confirm the association of serum Alkaline Phosphatase in Rheumatoid arthritis. Thus it can be concluded that estimation of serum Alkaline Phosphatase may be used as a biomarker for diagnosis and prognosis of Rheumatoid arthritis and may provide a useful tool for its management.

**Keywords:** Serum Alkaline Phosphatase, Rheumatoid Arthritis, Osteoclasts, Osteoblasts, Colorimetric.


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### INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disorder that may affect many tissues and organs, principally the joints. This process is based on imbalance between bone-resorbing osteoclasts and bone forming osteoblasts. The imbalance is caused by enhanced expression of inflammatory cytokines, such as tumor necrosis factor (TNF), which foster the differentiation of osteoclasts and hamper formation of osteoblasts. In consequence, repair of bone erosion is limited, with localized deposition of bone at the base of erosions (sclerosis)<sup>1</sup> and growth of small bony spurs.<sup>2</sup> The pathological findings in the joints include chronic non-suppurative, proliferative and inflammatory synovitis with formation of a pannus, which erodes cartilages, bones, ligaments and tendons. In the acute phase, effusion and other manifestations of inflammation are common. In the late stage organization may result in fibrous dysplasia. Although the cause of

RA remains unknown, autoimmunity plays a principal role in chronicity and progression.<sup>3</sup> Remodeling of bone is a continuous process throughout life. Resorption and formation of bone are normally tightly coupled. Changes leading to decreased rates of bone formation or increased rates of bone resorption or both may cause a decrease in bone mass. This involves a fine balance of the activity of osteoblasts and osteoclasts.

Alkaline phosphatase (ALP) is a hydrolase enzyme responsible for removing phosphate group from many type of molecules including nucleotide, proteins and alkaloids. As the name suggest, ALP are most effective in an alkaline medium. Bone Alkaline Phosphatase is the bone-specific isoform of ALP, a glycoprotein that is found on the surface of osteoblasts. BAP reflects the biosynthetic activity of these bone forming cells. It has been shown to be sensitive and specific marker of bone metabolism. Bone turnover may be

assessed by the measurement of enzymes or matrix proteins produced by osteoblasts or osteoclasts. The presence of ALP in the circulation may therefore provide a specific chemical index of osteoblastic activity. In fact the level of serum ALP is increased in disorders characterized by accelerated bone turnover.

For a long time, the diagnosis of RA was mainly based on clinical manifestations. However, it is often difficult to diagnose RA in very early phase of the disease and in many cases irreversible damage already occurred by the time diagnosis is confirmed. Therefore laboratory tests which are sensitive and specific early in the disease course are desirable to allow earlier diagnosis and intervention. This is the first study of serum alkaline phosphatase levels in Indian Manipuri population with Rheumatoid arthritis. Alkaline phosphatase may add useful information for assessing fracture risk and for monitoring osteoporosis in RA patients.<sup>4</sup>

### AIMS AND OBJECTIVES

To estimate the levels of Serum Alkaline Phosphatase in patients with Rheumatoid Arthritis and to compare it with that of controls.

### MATERIALS AND METHODS

A case control study was carried out in the Department of Biochemistry in collaboration with the Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India between Oct 2013 to Sep 2015. The study population consist of RA cases in the age group of 18 and above who were coming from different areas of Manipur and attending Rheumatology clinic

or admitted in the medical ward of RIMS, Imphal. Seventy six diagnosed case of rheumatoid arthritis irrespective of sex, caste and creed, who were willing to participate in the study voluntarily were included in this study. Patients with Paget's disease of bone, those suffering from osteoarthritis, psoriatic and reactive arthritis, hyperthyroidism or hyperparathyroidism were excluded from this study. Another 76 age and sex matched healthy subjects aged 18 years or above irrespective of sex, religion, socio-economic status were taken as controls.

A detailed history including name, age, sex, socio-demographic data, duration of disease, age of onset of disease was collected from each participant. Five ml of venous blood was drawn from each individual in a sterile plain vial, centrifuged immediately and was stored at 2-8°C. Prior to use, all the samples were kept at room temperature and tests were done within 24 hours. Serum Alkaline phosphatase was measured using colorimetric method using RX IMOLA by Randox Laboratories Ltd based on method described by Bowers GN and McComb RB.<sup>5</sup>

All the data collected was tabulated thereafter and statistical analysis was done using IBM SPSS statistics version 20 software. Data were expressed as Mean  $\pm$  SD. Statistical tests like  $\chi^2$ -test, independent t-test, ANOVA (F-test) were applied whenever found suitable and necessary. The P-value less than 0.05 was considered significant. Approval was sought from Institutional ethical subcommittee RIMS, Imphal. Consent was taken from each individual before taking blood samples. Confidentiality was maintained.

**Table 1: Age-wise distribution of Controls and Rheumatoid Arthritis Cases**

Age Group (in years)	Controls (n= 76)		Rheumatoid Arthritis cases (n=76)	
	Number	Percentage (%)	Number	Percentage (%)
< 40	12	15.79	7	9.22
41-50	13	17.10	10	13.15
51-60	33	43.42	41	53.95
61-70	16	21.05	12	15.79
> 70	2	2.64	6	7.89
<b>Total</b>	<b>76</b>	<b>100</b>	<b>76</b>	<b>100</b>

**Table 2: Sex - wise distribution of Controls and RA cases**

Sex	Controls		Rheumatoid Arthritis Cases	
	Number	Percentage (%)	Number	Percentage (%)
Male	27	35.52	22	28.95
Female	49	64.48	54	71.05
<b>Total</b>	<b>76</b>	<b>100</b>	<b>76</b>	<b>100</b>

### RESULTS

Table 1 show age-wise distribution of Rheumatoid arthritis cases and controls. Maximum no i.e. 41 (53.95%) of cases were in the age group of 51-60 years. This was followed by age group of 61 – 70 years with 12 (15.79%) cases. Similarly, maximum no. 33 (43.42%) controls belong to the age group of 51-60 years followed by 16 (21.05%) within the age group of 61-70 years.

Table 2 show Sex-wise distribution of controls and RA cases. Numbers of females are more in both the groups. Among cases, 54 (71.05%) were females as compared to 22 (28.95%) males.

Among controls number of males and females were 27 (35.52%) and 49 (64.48%) respectively.

Table 3 shows mean ( $\pm$  SD) for Serum Alkaline Phosphatase among RA cases and Controls. Serum Alkaline Phosphatase levels (cases-216.22  $\pm$  59.96IU/L, controls-164.17  $\pm$  50.67IU/L) were higher among Cases than controls. This difference was found to be statistically significant ( $p < 0.001$ ).

Table 4 shows the mean  $\pm$  SD values of Alkaline Phosphatase in both the groups according to sex. Females have higher value of

ALP among both controls and RA cases (169.90 ± 54.23 IU/L & 217.28 ± 64.07 IU/L respectively) compared to males (153.76 ± 42.55 IU/L & 213.61 ± 49.66 IU/L respectively). But this difference according to sex was not found to be statistically significant. However this difference was significant between males of both the groups (p < 0.001). Difference between

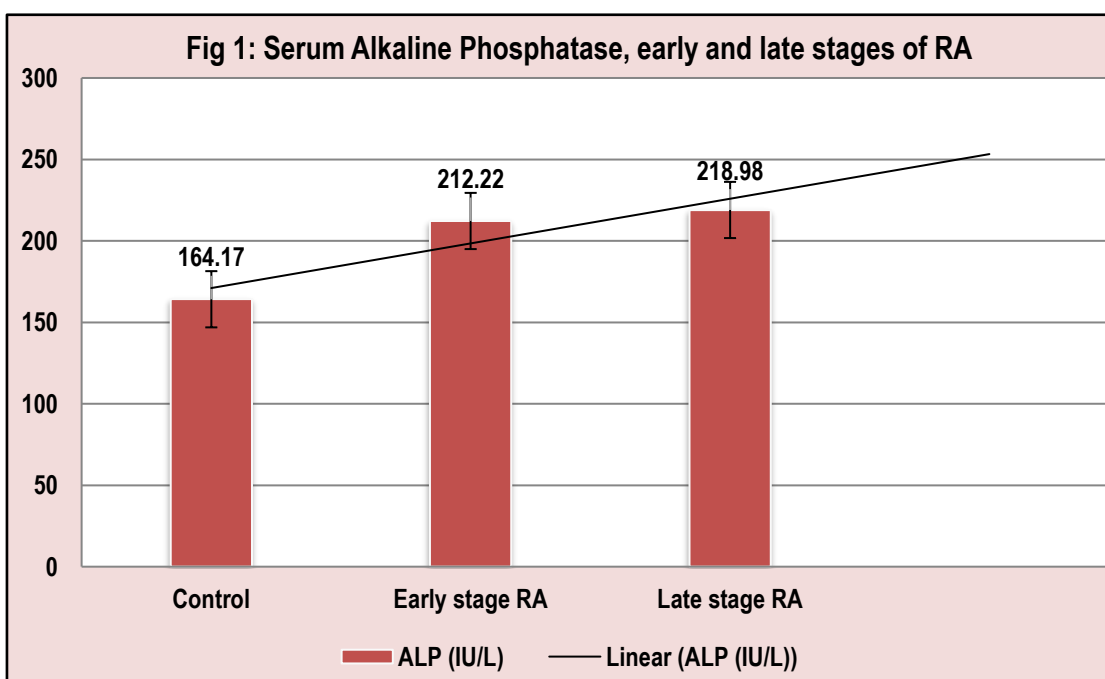
mean (± SD) was also significant between females of both the groups (p < 0.001). Fig 1 shows the values of serum alkaline phosphatase among controls, early and late stage of RA. The values of serum alkaline phosphatase increases significantly in both early and later stages when compared with control values.

**Table 3: Summary of ALP levels in Controls and RA Cases**

Parameter	Controls (Mean ± SD)	Rheumatoid arthritis Cases (Mean ± SD)	t	P value
Alkaline Phosphatase (IU/L)	164.17 ± 50.70	216.22 ± 59.96	5.78	< .001

**Table 4: Comparison of Serum ALP levels (Mean ± SD) in controls and RA cases by sex**

Sex	Serum ALP levels (IU/L)		t	P value
	Controls	RA Cases		
Male	153.76 ± 42.55	213.61 ± 49.66	4.54	< 0.001
Female	169.90 ± 54.23	217.28 ± 64.07	4.03	< 0.001



**DISCUSSION**

In the present study Rheumatoid arthritis was found to be most commonly prevalent among the adults in the age group of 51 – 60 years (53.95%), followed by the age group of 61-70 years with 15.79% cases and 41-50 years with 13.15% cases. The mean age was 54.57 ± 11.42 years with 55.00 ± 9.75 years for males and 54.39 ± 12.11 years for females. In our study, no significant difference was found in the mean age for both the sexes. This finding was similar with findings of Najeeb Q et al<sup>6</sup> and Georgiadis AN et al.<sup>7</sup> The disease was most prevalent in the middle aged population. In the present study females outnumbered males (68.42% and 31.58% respectively). Prevalence of RA was higher among females as compared to males. Value of Serum Alkaline Phosphatase among cases was 216.22 ± 59.96 IU/L as compared to controls 164.17 ± 50.67 IU/L. Significantly higher values of ALP have been found among RA cases as compared to controls. These findings were similar to the

findings of Magaro M et al.<sup>8</sup>, Aschenberg S et al.<sup>9</sup> and Vaithialingam A et al.<sup>10</sup> but contradictory to the findings of Klareskog L<sup>11</sup>, Jacobs JWG<sup>12</sup> and Gheita T.<sup>13</sup> Increased bone turnover is a feature of Rheumatoid Arthritis. Bone formation and resorption forms a coupling process of bone metabolism in which both components follow each other continuously.<sup>14</sup> When resorption is increased, so is formation. Similarly, when the former is decreased, the latter follows suit. Imbalance between these processes is responsible for increased or decreased bone mineral density and chances of complications due to it. RA is an inflammatory disease. It is characterized by chronic inflammation of the synovium, particularly of small joints, which often leads to destruction of articular cartilage and juxta articular bone. With cytokines mediated increased resorption of bone, bone formation also increase. This increased bone formation is correlated with increased Alkaline Phosphatase in patient serum.

Among both groups, females had higher values of Alkaline Phosphatase than males. But this difference were not significant in both the groups. However male RA patients had significantly (<0.001) higher values of ALP than males in control group. Similarly difference of ALP values among females of both the group was also significant. These findings were in consistent with Vaithialingam A et al<sup>10</sup> who also found noticeably increased levels of ALP among females than males but in their study which was statistically significant.

The mean  $\pm$  SD value of serum alkaline phosphatase increase significantly ( $p < 0.001$ ) in both early and late stage of RA cases when compared with controls. The parameter was higher in late stages of disease compared to early stages of the disease but this difference was not significant. However Gough AKS et al.<sup>15,16</sup> in their two studies found that patients with early RA had faster bone loss both at the lumbar spine and at the hip than that observed in a control group. Moreover, bone loss was slightly greater in the first year as compared with the second year of follow up. Conversely Shenstone BD et al.<sup>17</sup> who studied 67 patients with RA of less than 5 years duration and 72 controls over a 12-month period, found that bone loss was low (about 1%) and comparable in patients and controls. However, they also found that bone loss at the femoral neck was faster in those patients who had experienced onset of their disease less than 6 months earlier, as compared with the controls and the patients who had more long-standing disease.

## CONCLUSION

Increased bone turnover is a common feature of Rheumatoid arthritis. This study demonstrated that increased bone formation is associated with Rheumatoid arthritis together with bone resorption which affects the bone mineral density. The results of this study shows a significant increase in serum alkaline phosphatase level compared to controls which confirm the association of serum alkaline phosphatase with Rheumatoid arthritis. Thus it can be concluded that estimation of serum alkaline phosphatase levels may be used as a biomarker for diagnosis and prognosis of Rheumatoid arthritis and may provide a useful tool for its management.

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