Alkaline phosphatase isoenzyme activities in rheumatoid arthritis: hepatobiliary enzyme dissociation and relation to disease activity

Sumihisa Aida

Abstract

Objectives—Hyperphosphatasemia has been observed occasionally in patients with rheumatoid arthritis (RA), and it has been suggested that the serum alkaline phosphatase (ALP) level is related to the activity of the disease. Therefore, the relationship between serum ALP and RA was studied.

Methods—The serum activities of hepatobiliary enzymes (ALP isoenzymes, γ-glutamyltranspeptidase (GTP), leucine aminopeptidase (LAP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)), immunoglobulins, RA haemagglutinin test (RAHA), C reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were observed in 288 patients with rheumatoid arthritis.

Results—Serum biliary ALP (ALP1) activity was detected in 31.6% of the patients. In patients positive for ALP, the respective values of total ALP (ALPt) (p<0.001), liver ALP (ALPl) (p<0.001), bone ALP (ALP2) (p<0.005), γ-GTP (p<0.001), LAP (p<0.001), immunoglobulins IgG (p<0.01), IgA (p<0.01), and IgM (p<0.01), RAHA (p<0.001), CRP (p<0.001), ESR (p<0.001), and articular index (p<0.001) were significantly higher than in patients who did not have ALP. Significant Spearman’s rank correlations (rs) were demonstrated between serum ALP level and the respective values of ALPt (rs=0.9128, p<0.001), ALPl (rs=0.4443, p<0.001), ALP2 (rs=0.5898, p<0.001), γ-GTP (rs=0.2903, p<0.001), LAP (rs=0.3093, p<0.001), IgA (rs=0.2299, p<0.01), IgM (rs=0.1773, p<0.05), RAHA (rs=0.2426, p<0.01), CRP (rs=0.3532, p<0.001), ESR (rs=0.4108, p<0.001), and the articular index (rs=0.4006, p<0.001). However, no significant difference or correlation was noted for either AST or ALT. In many patients who showed abnormal hyperphosphatasemia, hepatobiliary enzyme dissociation was observed: levels of ALPt (in 12.8%), ALPl (in 31.6%), ALP2 (18.8%), γ-GTP (in 4.3%), and LAP (in 19.3%) were abnormally high, but both AST and ALT were within normal limits.

Conclusion—These findings are considered to be characteristic of RA, and suggest the existence of latent or subclinical hepatobiliary involvement and an association between the expansion of hepatobiliary involvement and the mechanism of disease activation. Thus measurement of the serum levels of ALP and its isoenzymes in RA is considered to be important.

The level of serum alkaline phosphate (ALP) in patients with rheumatoid arthritis (RA) is thought to be within normal limits. Hyperphosphatasemia has been observed occasionally in patients with RA, however, despite the absence of any clinical hepatobiliary disorder.1-12 Comparison between patients with RA and osteoarthritis has shown a higher serum ALP level in RA.1-12 These reports suggest an increase of the baseline serum ALP level in RA, although the underlying mechanism remains uncertain. Most reports have described that the raised serum ALP activity originates in the liver or bone, or both, from observations of ALP isoenzymes.6-11 Rosalki, Foo, and Tanner11 reported detection of serum biliary ALP isoenzyme (ALP1) activity, which is macro-molecular and is thought to be detectable only in cholestasis.13-15

Recently, observation of serum samples from patients with RA suggested that ALP1 activity was detectable at a high prevalence of about 30%.12 Furthermore, this report suggested that serum levels of liver ALP (ALPt) and bone ALP (ALP2) isoenzymes, as well as total ALP (ALPt) in patients with RA, were higher than in those with osteoarthritis, and that these levels in patients with RA who were ALP1 positive were higher than those who were negative. No ALP1 activity was detectable in serum samples from patients with osteoarthritis. Based on these findings, serum hepatobiliary enzyme activities in RA were observed in the present study. It is suggested that the serum ALP level is related to RA disease activity.1-3 5-12 The relation between serum ALP and RA disease activity was also studied, therefore, based on observations of immunoglobulins, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and articular index.15

Materials and methods

Two hundred and eighty eight patients with RA (226 women and 62 men; mean age, 54
Table 1 Cases demonstrating abnormal hyperphosphatasemia (more than 300 IU/l)

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>ALP* (IU/l)</th>
<th>ALP* (IU/l)</th>
<th>ALP* (IU/l)</th>
<th>γ-GTP* (U)</th>
<th>LAP* (U)</th>
<th>AST* (U)</th>
<th>ALT* (U)</th>
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ALPt=total alkaline phosphatase; ALP=biliary alkaline phosphatase; ALP=liver alkaline phosphatase; ALP=bone alkaline phosphatase; γ-GTP=γ-glutamyl transpeptidase; LAP=leucine aminopeptidase; AST=aspartate aminotransferase; ALT=alanine aminotransferase.

*Normal range: ALP=70–200 IU/l; ALP=10 IU/l; ALP<140 IU/l; ALP<110 IU/l; γ-GTP<60 U; LAP=103–190 U; AST=5–40 U; ALT=5–35 U.

Although abnormal values are seen in ALP, ALP, γ-GTP, and LAP, both AST and ALT are approximately within normal limits. ALP was measured by Bessey, Lowry, and Brock's method. The sum of ALP, ALP, and ALP is not equal to the value of ALP in some cases because intestinal ALP is not shown.

(SEE 1) years, diagnosed according to the revised criteria of the American Rheumatism Association, were entered into the present study. They had been receiving treatment for RA at our pain clinic from 1985 to 1991. The articular index was scored according to the method of Ritchie et al. No other diagnosed disorders were clinically evident in these patients, such as biliary, hepatic, skeletal, intestinal, or uterine diseases, and there was no overlap with other autoimmune or connective tissue diseases, such as systemic lupus erythematosus, or primary biliary cirrhosis. Non-steroidal anti-inflammatory drugs, corticosteroids, or disease modifying anti-rheumatic drugs had been given to all patients.

Figure 1 Left: relation between liver alkaline phosphatase (ALP) and total ALP (ALP). Significant Spearman's rank correlation (r) was demonstrated between ALP and each value of ALP (r=0.370; p<0.001), ALP (r=0.370; p<0.001), ALP (r=0.370; p<0.001), and γ-GTP (r=0.2903; p<0.001). Right: relation between ALP and γ-glutamyl transpeptidase (γ-GTP) (r=0.2903; p<0.001). Open symbols represent patients positive for ALP, and filled symbols, patients who had no ALP activity. The bar graph below the broken line (left) shows ALP in these patients negative for ALP. The values for patients positive for ALP are distributed to the upper right.
Alkaline phosphatase isoenzyme activities in RA

Figure 1  Relation between liver alkaline phosphatase (ALP) and IgA, IgM, or rheumatoid arthritis haemagglutination test (RAHA). Significant Spearman’s rank correlation (rs) were demonstrated between ALP and each value of IgA (rs=-0.2299; p<0.01), IgM (rs=-0.1773; p<0.05), or RAHA (rs=0.2420; p<0.01). Open triangles represent patients positive for biliary ALP (ALP1) and filled circles, patients with no ALP1 activity. The values of patients with ALP1 activity are distributed to the upper right.

All clinical assessments of articular index and laboratory data were performed as a routine clinical examination on the earliest consultation day after the start of this investigation in 1985, when informed consent was obtained. ALP activity was measured by the method of Bessey, Lowry, and Brock, and ALP isoenzymes were separated by electrophoresis on cellulose acetate membranes (Helena Laboratories, Urawa, Japan). Immunoglobulins (IgG, IgA, and IgM) were determined by single radial immunodiffusion (Hoechst Japan, Tokyo, Japan). Rheumatoid arthritis haemagglutination test (RAHA) was performed by the microtitre method (Fuji Reibo, Tokyo, Japan). An autoanayser (Hitachi 736-60, Hitachi Medico, Tokyo, Japan) and Clinimate kits (Daiichi Pure Chemicals, Tokyo, Japan) were used for measurements of ALP, γ-glutamyl transpeptidase (γ-GTP) (γ-glutamyl CPA substance method), leucine aminopeptidase (LAP) (Tuppy, Wiesbauer and Wintersberger’s method), aspartate aminotransferase (AST) (IFCC method), alanine aminotransferase (ALT) (IFCC method), and CRP (immunonephelometry). ESR was obtained by Westergren’s method.

The results were expressed as mean and standard error of the mean (mean ± SE). Data were analysed statistically using the Mann-Whitney U test, or Spearman’s rank correlation coefficient (rs). Differences at p<0.05 were considered significant.

Results

Serum ALP activity was detected in 91 out of 288 (32%) patients with RA and was undetectable in the remaining 198 patients. Values of ALP, varied from 2 to 497 IU/l, but 279 (97%) were less than 50 IU/l (table 1). In the patients positive for ALP, the respective values of ALP1 (p<0.001), ALP2 (p<0.001), ALP3 (p<0.05), γ-GTP (p<0.01), LAP (p<0.01), IgG (p<0.01), IgM (p<0.01), RAHA (p<0.001), CRP (p<0.001), ESR (p<0.001), and the articular index (p<0.001) were significantly higher, by the Mann-Whitney U test, than in those without ALP1 activity. No significant differences were noted in either AST or ALT (table 2).

On the other hand, significant Spearman’s rank correlations were demonstrated between the serum ALP1 level and the respective values of ALP1 (rs=0.9128, p<0.001), ALP2 (rs=0.4443, p<0.001), ALP3 (rs=0.5898, p<0.001), γ-GTP (rs=0.2903, p<0.001), LAP (rs=0.3093, p<0.001), IgG (rs=0.2299, p<0.01), IgM (rs=0.1773, p<0.05), RAHA (rs=0.2420, p<0.01), CRP (rs=0.3552, p<0.001), ESR (rs=0.4108, p<0.001), and the articular index (rs=0.4006, p<0.001). The values of these parameters in patients positive for ALP1 were distributed to the upper right, as shown in figs 1–3.

Many patients demonstrating hepatobiliary enzyme dissociation were noted: high values of ALP1, ALP2, γ-GTP, and LAP were seen in many patients, whereas the values of both AST and ALT were approximately within normal limits in all the patients tested (tables 1 and 3). No jaundice was observed in any of the patients. Table 1 shows the clinical data for 20 patients who demonstrated abnormally high serum ALP1 activity (more than 300 IU/l). Tables 1 and 3 suggest that hepatobiliary enzyme dissociation was demonstrated frequently for ALP1 (31–6%), often for ALP2 (12–8%), ALP3 (18–8%), and LAP (19–3%), and occasionally for γ-GTP (4–3%). However, four patients showing abnormal hyperphosphatasemia but ALP1 negativity were also noted. In these cases, the increase of ALP1 was not so severe, and ALP1 elevation was seen dominantly (table 1).

In a few cases a pattern considered to indicate binding to immunoglobulin was found. These cases showed electrophoretic patterns quite different from those of patients positive for ALP1 (fig 4), and were in agreement with the results obtained by Maekawa, Sudo, and Kano. Significant relations between the immunoglobulin binding and hepatobiliary enzymes were not noted.
Intestinal ALP isoenzyme activity was seen in the serum of type B or O blood, but this activity, 20 (SE 2) IU/l, was considered to be physiologically normal.21 No other ALP isoenzyme activity was seen.

Discussion

Hyperphosphataemia in patients with RA has been observed on occasion.1-12 Several authors have recorded a rise of ALP activity \(^{4, 8, 11, 12}\) accompanied by concurrent increases in \(\gamma\)-GTP\(^{4, 8, 12}\) or 5'-nucleotidase,\(^{7, 8}\) or both, but normal AST and ALT levels.\(^{5, 8, 12}\) On the other hand, it has been reported that serum ALP\(_1\) activity is detectable in patients with RA.\(^{11, 12}\) In the present study serum ALP\(_1\) activity was detectable in 31-6% of patients examined. This prevalence rate is thought to be very high, because serum ALP\(_1\) activity is usually detectable only in biliary disorders, as the internal pressure of the bile capillaries increases.\(^{11, 15}\)

In the present study high serum values of hepatobiliary enzymes were evident in many patients (tables 1 and 3). Significant correlations between ALP\(_2\), and the respective values of ALP\(_1\), ALP\(_2\), ALP\(_3\), \(\gamma\)-GTP, and LAP were demonstrated (fig 1), and these values were higher in those patients positive for ALP\(_1\), than in those who had no ALP\(_1\) activity. These findings indicate the probable existence of subclinical hepatobiliary involvement in RA. This involvement is supported by the histopathological observations by Kendall, Cockel, and Hawkins,\(^8\) Webb et al,\(^9\) Lefkovits and Farrow,\(^26\) and Dietrichson et al,\(^27\) indicating that the histology of the liver in RA is non-specific, and includes findings of Kupffer cell hyperplasia, fatty infiltration, and infiltration of peripheral areas with mononuclear cells.\(^28\)

Neither AST nor ALT was high, however, even in patients who showed abnormally high levels of ALP\(_1\), ALP\(_2\), and \(\gamma\)-GTP, and LAP in the present study (tables 1-3). These phenomena are considered to indicate hepatobiliary enzyme dissociation.

In the previous study,\(^12\) the baseline serum ALP\(_2\) level was significantly raised, even in patients without ALP\(_1\), in comparison with patients with osteoarthritis. In the patients positive for ALP\(_1\), the respective values of ALP\(_2\), ALP\(_3\), \(\gamma\)-GTP, and LAP were significantly higher than in patients without ALP\(_1\) activity (table 2). These results suggest more frequent underlying subclinical hepatobiliary involvement in RA than is generally assumed. Because the serum levels of these enzymes are known to increase more in biliary tract disorders than in hepatocellular injury,\(^\text{11-15}\) this involvement seems to start from the biliary capillaries at the latent stage. As involvement of the bile capillaries proceeds further, ALP\(_1\) leaks into serum and the serum ALP\(_1\) activity may be detectable. Concomitantly, the ALP\(_2\) level still rises. The leakage seems not to be attributable to an increase in internal pressure of the bile capillaries but to an increase in the permeability of the bile capillaries in RA. If the pressure had increased, jaundice would accompany the presence of ALP\(_1\). Even in the case showing a very high level of ALP\(_2\)—that is, 1756 IU/l (ALP\(_1\), 497; ALP\(_2\), 787 IU/l), jaundice was not observed. Thus ALP\(_2\), \(\gamma\)-GTP, and LAP increase considerably, as shown in fig 1, but remain at subclinical levels in most cases (table 2). Considering the normal levels of both AST and ALT at this stage, therefore, hepatocellular injury is thought to be slight. When the involvement expands to hepatocytes, obvious hepatitis, such as that

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Table 3: Hepatobiliary enzyme dissociation

<table>
<thead>
<tr>
<th></th>
<th>ALP(_1) (n=288)</th>
<th>ALP(_2) (n=288)</th>
<th>ALP(_3) (n=288)</th>
<th>(\gamma)-GTP (n=223)</th>
<th>LAP (n=223)</th>
<th>AST (n=258)</th>
<th>ALT (n=258)</th>
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<tr>
<td>(n)</td>
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<td>54</td>
<td>11</td>
<td>43</td>
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</tr>
<tr>
<td>(%)</td>
<td>12.8</td>
<td>31.6</td>
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<td>191-871</td>
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ALP\(_1\)=total alkaline phosphatase; ALP\(_2\)=biliary ALP; ALP\(_3\)=liver ALP; \(\gamma\)-GTP=\(\gamma\)-glutamyltranspeptidase; LAP=leucine aminopeptidase; AST=aspartate aminotransferase; ALT=alanine aminotransferase.

Although high values are demonstrated in ALPs, ALP\(_1\), ALP\(_2\), \(\gamma\)-GTP, and LAP of many patients with RA, both AST and ALT are approximately within normal limits.

*Values of AST were less than 40 U in all patients.
Alkaline phosphatase isoenzyme activities in RA

Figure 4  Electrophoretic patterns of serum alkaline phosphatase in patients with rheumatoid arthritis. A: normal pattern. B: a pattern considered to indicate binding to immunoglobulin. C and D: biliary ALP (ALP3) activity is evident. ALPv has moved towards the anode side.

reported by Job-Deslande et al.29 may become clinically evident. Of course, the levels of AST and ALT would then increase. However, Job-Deslande et al.29 demonstrated that increases in serum bilirubin (10–63 \( \mu \)mol/l), AST (54–92 U), and ALT (54–152 U) were mild in hepatitis during RA, and jaundice was present in two of six cases. These facts are thought to support the results of the present study. Therefore, it is thought that we observed the latent or subclinical involvement of RA as hepatobiliary enzyme dissociation. Such dissociation, which is considered to be characteristic of RA, was observed frequently for ALP, sometimes for ALPt, ALP+, and LAP, and occasionally for \( \gamma \)-GTP, and became more frequent in the patients positive for ALP, (tables 1 and 3). The number and level of parameters showing abnormal values are thought to indicate the grade and intensity of hepatobiliary involvement.

A connection between serum ALP and RA disease activity has already been shown by several authors.1-3 5-12 In the present study significant correlation between ALP and the respective values of IgA, IgM, RAHA, CRP, ESR, and the articular index was demonstrated (figs 2 and 3), and IgG, IgA, IgM, RAHA, CRP, ESR, and the articular index in patients positive for ALP, were all significantly raised compared with patients without ALP, activity (table 2). These facts suggest a relation between the two phenomena in hepatobiliary involvement and disease activation.

It is known that promotion of disease activity induces more active bone resorption.21 32 Activated bone resorption is accompanied by concomitant bone formation and a rise in serum ALP.21 Therefore, several authors1-3 5-7 10 have considered that disease activity in RA is related to the level of ALP. A relation between RA disease activity and ALP, might not be wholly denied. The higher ALP, level in patients with RA, however, is considered to be produced by the activated bone formation: this is to say, a rise of ALP is not a cause but a result of disease activation. Therefore, a significant correlation between ALP, and ALP, was considered to be present (fig 1). In four patients negative for ALP, showing abnormal hyperphosphatasaemia, however, the ALP, level was considerably raised (patients 1–4 in table 1). From these facts, the existence of other disease activation mechanisms, which are not associated with hepatobiliary enzyme dissociation, is also suggested. In actual cases, both mechanisms would work concurrently. Whichever mechanism operates, serum ALPt activity may have to increase in parallel with disease activity in RA. In fact, three of these four patients also had a high ALP, level (table 1). Therefore, ALP1, ALP2, and ALP, are considered important for the evaluation of disease activation. To determine whether the disease activity is associated with ALP activities, however, other markers that directly indicate the disease activity should be monitored in the long term.

There is also a possibility that rises in ALP, \( \gamma \)-GTP, and LAP are due to liver toxicity resulting from treatment with non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs, or corticosteroids. In the present study, however, no pathological increase of AST and ALT was observed in any subject even though treatment with these drugs was continued. The previous study12 also showed that this was unlikely, as ALP isoenzyme activities did not differ among patients treated with these drugs. Doube et al.30 also reported that non-steroidal anti-inflammatory drugs had no influence on ALP activity in patients with RA. Therefore, rises in these enzymes are considered to be attributable to RA itself.

Webb et al.,3 Spooner et al.,3 and Kantharia and Woolf3 demonstrated cases of RA and primary biliary cirrhosis overlapping. In the present study, however, patients with apparent hepatobiliary disorders, such as cirrhosis or hepatitis, were excluded and both AST and ALT were at normal levels. Thus the present findings indicate that serum biliary enzymes, especially ALPt, ALP1, and ALP2, are related closely to the activity of RA and subclinical hepatobiliary involvement by RA, which is observed in the latent and subclinical stages as hepatobiliary enzyme dissociation.

Rosalki 16  
Ritchie 13  
Tuppy 14  
Brocklehurst D, Bessy 17  
Cimmino 10  
Crofton 19  
Siede 6  
Fernandes 516  


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S Aida

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