CLEVELAND CLINIC QUARTERLY
Volume 35, July 1968

Printed in U.S.A.

Lack of diagnostic significance of serum alkaline phosphatase values in differentiating hepatocellular and obstructive jaundice

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ELEVATION of serum alkaline phosphatase values occurs in a number of diseases associated with osteoblastic activity, as well as in obstructive, infiltrative, and parenchymal diseases of the liver and the biliary tract. The report of Roberts,[1] in 1930, that serum alkaline phosphatase values were elevated in patients with obstructive jaundice, attracted considerable attention. Since then the serum alkaline phosphatase content has been used widely in the differential diagnosis of jaundice.

Great increase in serum alkaline phosphatase content has been thought to be indicative of obstructive jaundice. When there are highly elevated values in hepatic disease, the physiologic mechanism has been considered "biliary obstructive" in nature, as in cholangiolytic hepatitis and biliary cirrhosis. Roberts,[1] and Rothman, Meranze, and Meranze[2] believed that there was a sharp demarcation in this regard between obstructive and hepatocellular jaundice. They found values greater than 10 units per 100 cu mm (modified Roberts' method) in 25 of 29 patients with obstructive jaundice, and 10 units or less in 18 of 24 patients with hepatocellular jaundice. In differentiating between these two types of jaundice, Sherlock[3] preferred an arbitrary dividing line of 30 King-Armstrong units. She believed that in obstructive jaundice, levels are usually more than 30 King-Armstrong units or 10 Bodansky units, and that in hepatocellular jaundice they are usually less than 30 King-Armstrong units. She stated that "Unusually low levels in obstructive jaundice are more frequent than unexpectedly high values in hepato-cellular jaundice." Cantarow and Nelson[4] found wide overlapping of alkaline phosphatase values in ob-

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structive and hepatocellular types of jaundice, and concluded that this serum factor was of no value in differentiating between these two types of jaundice.

Our attention was drawn recently to the possible diagnostic significance of serum alkaline phosphatase content by finding extremely high values in several patients with hepatocellular disease, with no evidence of biliary obstruction. To evaluate the diagnostic worth of the values, a group of 200 consecutive patients, selected on the basis that in each the serum alkaline phosphatase value was 25 or more King-Armstrong units, were studied.

METHOD

Two hundred consecutive patients comprised the series in this study, in each of whom the serum alkaline phosphatase value was 25 or more King-Armstrong units. The absence of jaundice was not an excluding factor. All patients were adults and were outpatients or were in the Cleveland Clinic Hospital. Serum alkaline phosphatase content was determined by means of the AutoAnalyzer and a modification of the Bessy-Lowry-Block technic. In this method, p-nitro phenyl phosphate with a pH of 10.4 is used as the substrate, at a temperature of 37 C. On hydrolysis, the p-nitro phenol released is measured colorimetrically. The standards of p-nitro phenol have been based on Versatol E to give the appropriate King-Armstrong units. In the 200 patients the serum alkaline phosphatase concentrations ranged from 25 to 320 King-Armstrong units. Only 17 patients had values between 25 and 30 King-Armstrong units; 130 (65 percent) had values of more than 50 King-Armstrong units.

Accurate diagnoses, essential in such a study, were established by one or more of the following procedures: needle biopsy of the liver (50 patients), laparotomy and biopsy (58 patients), laparotomy (59 patients, most of whom had obvious biliary obstruction), and lymph node biopsy (3 patients). Diagnosis was made on the basis of the clinical manifestations without tissue diagnosis in 30 patients (most of whom had nonhepatic diseases) with elevated serum alkaline phosphatase values. Patients were classified according to five disease groups.

Group I, 51 patients

Hepatocellular diseases:

(a) Biliary cirrhosis	8
(b) Other types of cirrhosis (postnecrotic, nutritional, portal, cardiac, and fatty liver)	25
(c) Hepatitis (viral or serum, and infectious mononucleosis)	8
(d) Cholangiolytic hepatitis	3
(e) Drug-induced hepatitis	4

(f) Miscellaneous hepatic diseases (1 amyloid, 1 sarcoid, and 1 case of granulomatous infiltration of the liver) 3

Group II, 52 patients

Extrahepatic obstructive disease:

(a) Benign obstruction (stone, division, stricture of common bile duct) 27

(b) Malignant obstruction (cancer of ampulla of Vater, cancer of pancreas, and cancer of the common bile duct) 25

Group III, 41 patients

Metastatic hepatic neoplasms 41

Group IV, 24 patients

Skeletal diseases (including Paget's disease, prostatic, parathyroid, and breast neoplasms with bony metastases) 24

Group V, 32 patients

Miscellaneous 32

This group includes those patients without definite tissue diagnoses, those with poorly established diagnoses, and some of those with neoplastic disease affecting both the liver and the skeletal system.

RESULTS

Serum alkaline phosphatase values in the various groups were as follows (*Table 1 and Fig. 1*).

Table 1.—*The mean values and standard deviations of serum alkaline phosphatase values in patients in groups I, II, and III**

Group	Serum alkaline phosphatase, King-Armstrong units			
	Number of patients	Range	Mean value	Standard deviation
Group I (hepatocellular disease)	51	25–294	86.2	—
(a) Biliary cirrhosis	8	39–245	138.4	64.7
(b) Other types of cirrhosis	25	25–208	71.0	54.0
(c) Hepatitis	8	29–294	93.7	84.8
(d) Cholangiolytic hepatitis	3	28–167	79.7	76.0
(e) Drug-induced hepatitis	4	37–141	96.0	47.1
(f) Miscellaneous liver diseases	3	42–53	47.7	6.1
Group II (extrahepatic obstructive disease)	52	26–240	86.5	—
Benign	27	26–183	73.2	48.0
Malignant	25	41–240	99.8	48.4
Group III (hepatic neoplasm)	40	25–320	87.0	56.9

* No statistical investigations were made of groups IV and V.

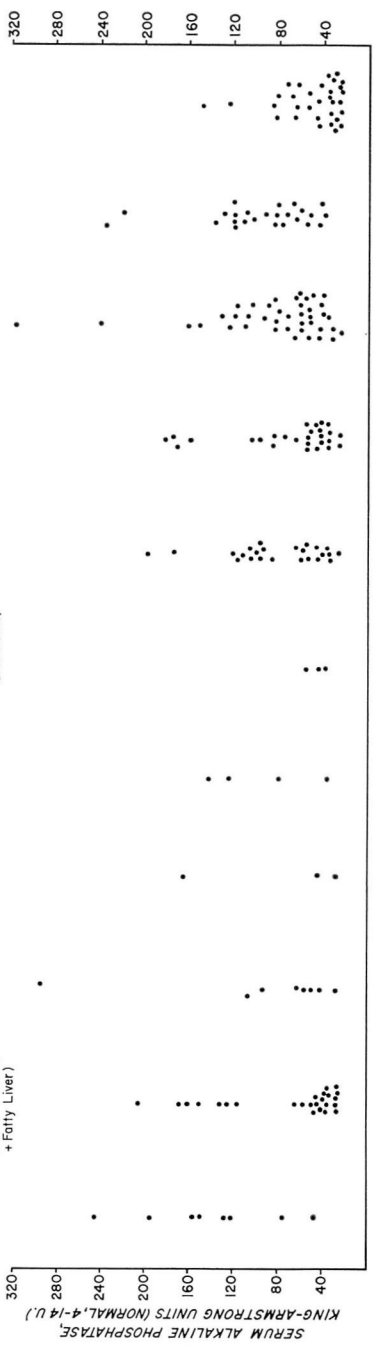

Fig. 1. Graph showing the serum alkaline phosphatase values in the various disease groups. Note especially the high values in the group with hepatocellular disease. Similar elevation was found in patients with obstructive jaundice.

Group I, hepatocellular diseases (a through f)

The mean value* for group I was 86.2 King-Armstrong units. The highest value (294) was observed in posttransfusional hepatitis, and the next highest (245) in biliary cirrhosis. Only seven patients (14 percent) of this group had serum alkaline phosphatase contents between 25 and 30 King-Armstrong units. In 21 patients (42 percent) the values were between 30 and 60, and in 23 patients (44 percent), between 60 and 294 King-Armstrong units.

Group II (extrahepatic obstruction)

The mean value for group II was 86.5 King-Armstrong units. In patients with malignant types of obstruction the highest values were 240 and 225, with a mean value of 99.8 King-Armstrong units. In the patients with benign types of obstruction, the highest value was 185, with a mean value of 73.2 King-Armstrong units.

In regard to benign forms of obstruction, only two patients had alkaline phosphatase values between 25 and 30 King-Armstrong units. In five patients the levels were between 30 and 60; in 10 patients the levels were between 60 and 185 King-Armstrong units. In malignant types of obstruction, no values were less than 40 King-Armstrong units. In five patients the levels were from 40 to 60; in 20 patients the levels were from 60 to 240 King-Armstrong units.

Group III (metastatic hepatic neoplasm)

The mean value for group III was 87.0, the highest value was 320 King-Armstrong units. In one patient the serum alkaline phosphatase content was between 25 and 30 King-Armstrong units. In 14 patients (33 percent), the content was between 30 and 60; in 26 patients (65 percent) the content was between 60 and 320 King-Armstrong units.

Groups IV and V. In these two groups, no detailed statistical investigations were made.

The results show that the difference between the mean values of serum alkaline phosphatase in the "hepatocellular group" (86.2) and in the "obstructive group" (86.5) is only 0.3 King-Armstrong unit. This difference is not significant by the "t" test, which was used for our statistical analysis. There was a lack of significant difference even when patients with biliary cirrhosis and cholangiolytic hepatitis were excluded from the hepatocellular group.

The correlation coefficient between the serum alkaline phosphatase and

** The statistical analysis was made by J. N. Berrettoni, Ph.D., Chairman, Department of Statistics, Case-Western Reserve University, Cleveland, Ohio.*

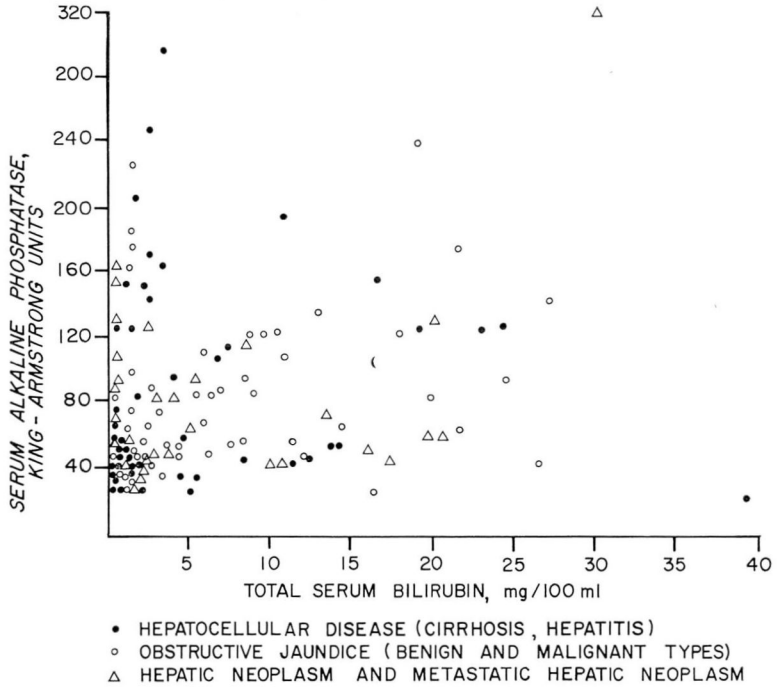

Fig. 2. Graph showing the only slight correlation of the level of the serum bilirubin and that of the serum alkaline phosphatase. The lack of any relationship between the two values and the disease group is apparent.

the serum bilirubin values in the 132 jaundiced patients in our series was 0.232 (*Fig. 2*). This low correlation coefficient shows some relationship between the elevation of bilirubin and alkaline phosphatase, but is too low to be of practical significance. A high serum alkaline phosphatase content and a relatively normal serum bilirubin content were associated with hepatocellular disease as frequently as with biliary obstruction, and vice versa.

Becker and Stauffer[5] obtained similar results in a study of 200 jaundiced patients, of whom 100 had hepatitis and 100 had obstructive jaundice. Ninety-three percent of the patients with obstructive jaundice and 40 percent of those with hepatitis had elevations of serum alkaline phosphatase content greater than 30 King-Armstrong units; conversely, 7 percent of the patients with obstructive jaundice and 60 percent of those with hepatitis had values less than 30 King-Armstrong units. The authors[5] found no correlation between the serum bilirubin and serum alkaline phosphatase values of the two diseases. They concluded that elevation of the serum alkaline phosphatase had no diagnostic significance in differentiating hepatocellular from obstructive jaundice, but that a normal alkaline phosphatase value in the presence of jaundice was suggestive of hepatocellular disease.

Discussion

Our findings and those of Becker and Stauffer[5] are in disagreement with those of Maclagan,[6] who reported that the elevation of the serum alkaline phosphatase value was not so high as we found. In 92 percent of 110 patients with hepatitis in Maclagan's series; two thirds were between 12 and 30; one third were more than 30, and only 5 percent were more than 45 King-Armstrong units.

In our study, of 51 patients with hepatocellular disease, 23 (44 percent) had values between 60 and 294 King-Armstrong units. The mean value in group I for combined (b) cirrhosis (other than a biliary type) and (c) hepatitis (other than the cholangiolytic type) was 76.52 King-Armstrong units; and for extrahepatic obstructive disease was 86.50; a difference of 9.98 King-Armstrong units, which again was not significant by the "t" test. In our study, the serum alkaline phosphatase levels in patients with viral and toxic hepatitis were considerably higher than those reported by Schiff.[7]

One explanation for the difference between our results and those of Schiff[7] and others is that we excluded all patients with serum alkaline phosphatase values less than 25 King-Armstrong units; undoubtedly a moderate number of patients with hepatocellular disease were not included in our study. Our study concerns the diagnostic significance of elevation of the serum alkaline phosphatase value and what a moderately high value may mean to the clinician. Consequently, we purposely included in our study only patients with serum alkaline phosphatase values of more than 25 King-Armstrong units.

The question arose as to whether there might or might not be a relationship between the serum alkaline phosphatase content and the serum glutamic oxaloacetic transaminase (SGOT) content. Statistical analyses of these data and correlation coefficients in this regard were not determined. However, a chart (*Fig. 3*) showing the serum alkaline phosphatase values plotted against the SGOT values suggests a lack of correlation between elevated values of the two enzymes. It should be noted that the highest values for SGOT were in those patients with hepatocellular disease.

It is of interest that biliary obstruction resulting from carcinoma produced higher values of the serum alkaline phosphatase than those in patients with benign lesions producing obstruction, but there was considerable overlapping of values. Maclagan[6] emphasized that patients with levels greater than 75 King-Armstrong units should be tentatively considered to have obstructive jaundice. Our findings do not support this concept.

West and Zimmerman[8] indicated that Laennec's cirrhosis is characterized by normal or slightly elevated serum alkaline phosphatase values. In our series, levels of 126 and 169 King-Armstrong units were in patients with Laennec's cirrhosis. Also, the mean value of 70 King-Armstrong units among the 25 patients with cirrhosis (other than a biliary type), in our series, indi-

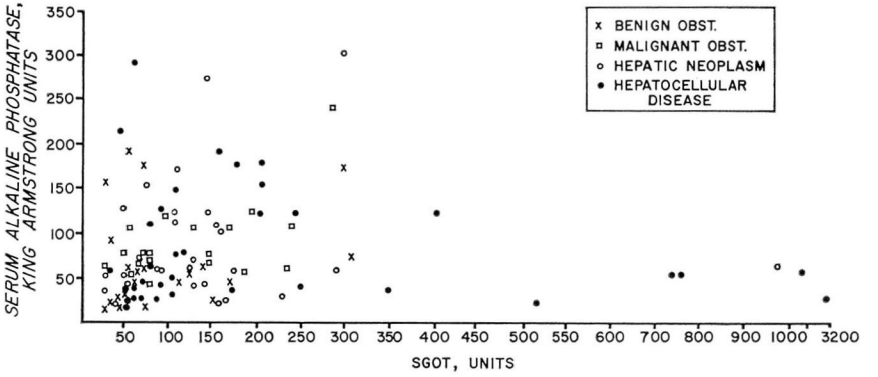

Fig. 3. Graph showing the relationship between the serum alkaline phosphatase and the SGOT values by the major disease categories. A high elevation in SGOT content was obtained in some patients with hepatocellular disease with only moderate elevation of the serum alkaline phosphatase content; otherwise there did not appear to be any relationship.

cates that the serum alkaline phosphatase content may be greatly increased in Laennec's and in postnecrotic cirrhosis. Some clinicians believe that in obstructive jaundice the serum alkaline phosphatase activity and serum bilirubin concentration increase proportionately until the limit of alkaline phosphatase is reached—120 to 180 King-Armstrong units.[9] According to *Figure 2,* this proportionate increase did not take place in our series.

Great elevation of the serum alkaline phosphatase value in the absence of jaundice can be suggestive of carcinoma metastatic to the liver, if bone disease and metastasis can be excluded. The basis for elevation of serum alkaline phosphatase content in patients with space-occupying lesions (such as metastatic or primary carcinomas) of the liver is not clear. Brem[10] suggested that such hepatic lesions may provoke the elevation of serum alkaline phosphatase content by means of compression of the contiguous intrahepatic ducts. In the experience of West and Zimmerman,[8] 92 percent of the patients with metastatic carcinoma of the liver had elevated serum alkaline phosphatase values when the metastases were sufficiently extensive to produce hepatomegaly. Bockus[11] suggested that carcinoma of the liver may be detected as a complication by an increased serum alkaline phosphatase content greater than the usual levels associated with underlying cirrhosis.

SUMMARY

Two hundred consecutive patients in each of whom the serum alkaline phosphatase level was 25 or more King-Armstrong units were studied. In 65 percent of the patients the serum alkaline phosphatase levels were more than 50 King-Armstrong units. The concentrations ranged from 25 to 320 King-Armstrong units.

The patients were classified according to five groups on the basis of histopathologic diagnoses. The degree of elevation of serum alkaline phosphatase content had no differential diagnostic significance, as there was only a slight difference between the levels in patients with hepatocellular disease and in those with biliary obstruction. The serum alkaline phosphatase content was increased in 41 patients with hepatic neoplasm, and in 24 patients with skeletal disease.

No significant correlation was found between the serum alkaline phosphatase and the serum bilirubin values. Discrepancies between the bilirubin and alkaline phosphatase values were frequent and had no diagnostic significance.

In regard to the elevated serum alkaline phosphatase values, no distinction can be drawn between hepatocellular and obstructive types of jaundice. From our study, elevation of the serum alkaline phosphatase content per se appears to be of little value in the differential diagnosis of hepatocellular jaundice and obstructive jaundice.

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