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ORIGINAL ARTICLE

SERUM ENZYMES IN HEPATOBILIARY CARCINOMA

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ABSTRACT: INTRODUCTION: Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Hepatic metastasis occurs in 40-50% of adult patients with extrahepatic primary malignancies. The levels of enzymes alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and leucine aminopeptidase (LAP) are deranged in pathological conditions. **AIM**: To study and compare the serum enzymes Alkaline phosphatase (ALP), Gamma-glutamyl transpeptidase (GGT) and Leucine aminopeptidase (LAP) in cases of hepatobiliary carcinoma. **METHODOLOGY**: 30 patients diagnosed with heptobiliary carcinoma were enrolled for the study and 50 healthy individuals of matched age and sex served as controls. Serum Leucine Aminopeptidase (LAP), Alkaline Phosphatase (ALP) and Gamma-glutamyl Transpeptidase (GGT) were determined and compared in study and control groups. **RESULTS**: The mean levels of serum ALP, GGT and LAP in the study group were 786.3±465.05 IU/L, 193.3±116.73 IU/L and 96.86±34.74 IU/L respectively. These values were significantly higher than in the control groups. Serum LAP showed abnormal levels in maximum number of cases (93.3%) followed by serum GGT in 83.3% and serum ALP in 76.6% cases. ALP, GGT and LAP levels were significantly higher in icteric and nonicteric groups as compared to control group. **CONCLUSIONS**: Serum ALP, GGT and LAP were significantly elevated in the patients with hepatobiliary carcinoma and the elevations were significantly higher in icteric as compared to nonicteric groups. Serum LAP is a better indicator of hepatobiliary carcinoma.

KEYWORDS: ALP, GGT, LAP, Hepatobiliary Carcinoma.

INTRODUCTION: Hepatobiliary carcinoma includes carcinoma of liver, pancreas, bile ducts, ampulla of Vater and gall bladder. Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. It is the fourth most common cancer in the world[1]. Metastases are the most common malignant tumors of the liver[2]. Metastasis of liver is commonest ranking second only to cirrhosis as a cause of liver damage. The incidence of carcinoma of the pancreas has markedly increased over the past several decades and ranks as the fourth leading cause of cancer death in the United States[3]. In pathological conditions there is usually some derangement in the metabolic processes which is reflected by a change in enzymatic patterns. The detection of these biochemical agents is simple and noninvasive.

Leucine aminopeptidase (LAP, 3.4.11.1), a proteolytic enzyme, is capable of hydrolyzing L-Leucyl peptides and is primarily involved in protein digestion in small intestine mucosa. LAP is widely distributed in bacteria, plants and distributed in all human tissues with high activity in liver as well as in duodenum, small intestine, pancreas, testis and stromal cells of the uterus[4]. This enzyme is an integral membrane glycoprotein located to apical domain of intestinal epithelial cells. Serum alkaline phosphatase (ALP, 3.1.3.1) is a phosphomonoesterase, which has a widespread distribution in body tissues and is also synthesized in the ductal epithelium in liver. Elevation of serum alkaline phosphatase in liver disease occurs primarily in cholestatic disorders. Gamma glutamyl

transpeptidase (GGT, 2.3.2.1), is an enzyme located in the membrane of cells which show high secretory or absorptive capacity like epithelial cells lining the biliary tract, hepatic canaliculi, pancreatic acinar tissue, and intestinal brush border cells[5]. GGT participates in transport of amino acids across intracellular membranes as part of gamma glutamyl cycle. In cases of elevated serum levels of gamma glutamyl transpeptidase, the largest contribution is from liver, with little from kidney, pancreas and intestine[6]. The present study attempts to assess the usefulness of serum enzymes alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and leucine aminopeptidase (LAP) in the diagnosis of hepatobiliary carcinoma.

MATERIALS AND METHODS: The study was done on 30 patients diagnosed with heptobiliary carcinoma visiting surgery and medicine department of Govt. Medical College and Hospital, Patiala. The study was approved by college ethical committee. 50 healthy aged and gender matched adults served as control. Clinically proven cases of hepatobiliary carcinoma, confirmed on radiological investigations, laparotomy, ultrasound, CT scan or MRI were included in the study group. Detailed history was taken and a thorough clinical examination was done. The study group was further divided into icteric and non- icteric groups. All cases which had received chemotherapy, gave history of bone fracture or bone disease in last six months, children, pregnant women and chronic alcoholics were excluded from the study. Serum Leucine Aminopeptidase, Alkaline Phosphatase and Gamma-glutamyl transpeptidase were determined using optimized kinetic method.

Investigations done were Hemoglobin (Hb), Total leucocyte count (TLC), Bleeding time(BT), Clotting time (CT), Erythrocyte sedimentation rate (ESR), Fasting blood sugar (FBS), Blood urea, Serum creatinine, TSP, DSP (serum albumin and glopulin), serum amylase, serum bilirubin, Aspartate Transaminase(AST) and Alanine Transaminase(ALT). Serum leucine aminopeptidase (LAP) was determined by optimized kinetic method according to the recommendations of the German society of Clinical Chemistry[7]. When L-leucyl-p-nitroanilide is acted upon by the enzyme leucine aminopeptidase, p-nitroaniline is liberated.

The absorption of p-nitroaniline is very high at 405 nm, whereas the substrate hardly absorbs at all at this wavelength. The absorbance is read at 405 nm and is directly proportional to the enzyme activity. Reagents: Buffered substrate solution (1.6 mM in 0.05M tris Buffer, pH- 7.2): 40.2 mg of L-leucyl-p-nitroanilide was dissolved in 2 ml of 96% ethanol and made upto 100 ml with tris buffer. The freshly prepared solution had an absorbance between 0.090 and 0.095 against distilled water at 405 nm. Reagent was freshly prepared each time and was stored in dark colored bottle. Serum ALP was measured by kinetic method and the kit was supplied by Accurex Biomedical Pvt. Ltd., Mumbai. For GGT, the methodology used was of Ssaz[8], using single reagent chemistry by kinetic (IFCC) method and the kit used was supplied by Erba/transasia Biomedical Pvt. Ltd., Mumbai. Serum levels were again estimated and compared after one month of treatment in the form of surgery, radiotherapy or chemotherapy.

RESULTS: There was no statistical significant difference in the mean age and sex distribution of study and control groups. Loss of appetite and weight were the main presenting symptoms. (Figure I).Distribution of patients according to diagnosis is depicted in Figure 2. The study group was further divided into icteric and non-icteric groups depending upon the presence or absence of icterus (Figure 3). Serum bilirubin, AST and ALT were found to be significantly higher in study group as compared to

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control group (Table 1). The mean levels of serum ALP, GGT and LAP in the study group before initiation of treatment were 786.3±465.05IU/L, 193.3±116.73IU/L and 96.86±34.74 IU/L respectively. These values were significantly higher than in the control group (Table 2). Out of 30 patients of hepatobiliary carcinoma, serum LAP showed abnormal levels in maximum number of cases (93.3%) followed by serum GGT in 83.3% and serum ALP in 76.6% cases (Table 3).

Thus, it is observed that out of the three enzymes, serum LAP is the most sensitive index of hepatobiliary carcinoma. Levels of all the three enzymes i.e., ALP, GGT and LAP were significantly higher in icteric and non-icteric groups as compared to control group. Also, icteric group showed higher values than the non-icteric group, the difference being highly statistically significant (tables 4 and 5). LAP was significantly raised ($p<0.001$) in the icteric as compared to the non-icteric group. 15 out of 16(93.75%) nonicteric cases had elevated LAP.

This was followed by GGT, raised in 12/16(75%) nonicteric cases and ALP raised in just 9/16(56.25%) nonicteric cases. (Table 6). Therefore, it is observed that LAP is the most frequently elevated enzyme in non-icteric patients. The serum levels of ALP, GGT and LAP before and after treatment are compared in table 7. Out of 30 patients in the study group, only 26 could be followed up because three patients had expired and one refused to follow-up. Though the mean levels of all three enzymes decreased on the follow-up, the difference was not significant statistically.

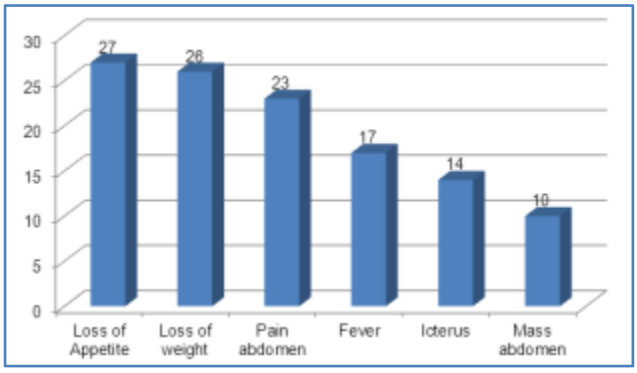

Fig.1: showing distribution of patients according to general presenting symptoms

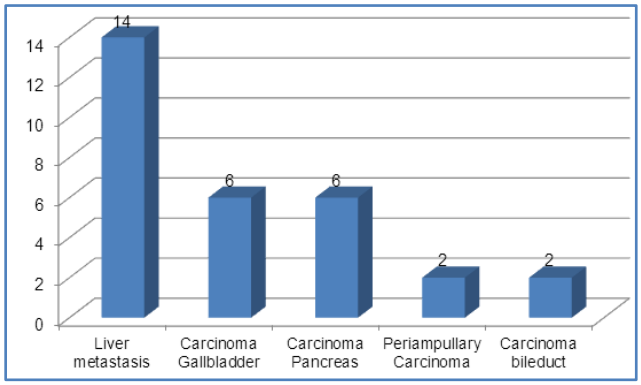

Fig. 2: showing distribution of patients accordingto diagnosis

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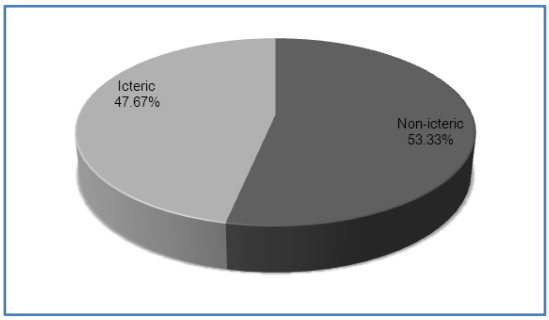

Fig. 3: showing icteric and nonicteric cases of study group

Parameter	Group	Range	Mean±SD	t	p	Significance
Bilirubin (mg %)	Study	0.4-14.2	3.15±3.65	5.16	<0.001	HS
	Control	0.1-0.9	0.48±0.19			
AST (IU/L)	Study	30-220	107.3±70.14	8.63	<0.001	HS
	Control	10-35	21.26±7.4			
ALT (IU/L)	Study	18-160	67.83±49.60	6.30	<0.001	HS
	Control	12-32	23.18±6.32			

Table 1: showing serum Bilirubin, AST and ALT levels in study and control groups

Enzyme	Group	No. of Patients	Range (IU/L)	Mean±SD (IU/L)	t	p	Significance
ALP	Study	30	220-1650	786.3±465.05	9.51	<0.001	HS
	Control	50	112-240	159.48±38.05			
GGT	Study	30	30-410	193.3±116.73	10.74	<0.001	HS
	Control	50	8-42	16.02±7.55			
LAP	Study	30	36-176	96.86±34.74	12.87	<0.001	HS
	Control	50	27-40	33.02±4.41			

Table 2: Comparison of serum ALP, GGT and LAP levels in study and control groups.

Level of Enzyme	ALP		GGT		LAP	
	No.	% age	No.	% age	No.	% age
Normal	7	23.33	5	16.67	2	6.67
Above normal	23	76.67	25	83.33	28	93.33
Total	30	100	30	100	30	100

Table 3: Showing frequency of elevation of serum ALP, GGT and LAP in study group

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Enzyme	Values (IU/L)	Control (C) (n=50)	Icteric (I) (n=14)	Non-icteric (NI) (n=16)
ALP	Range	112-240	880-1650	220-860
	Mean±SD	159.48±38.05	1215.42±258.83	410.81±194.45
GGT	Range	8-42	42-410	30-340
	Mean±SD	16.02±7.55	271.78±100.78	124.62±82.23
LAP	Range	27-40	38-176	36-150
	Mean±SD	33.02±4.41	116.71±31.64	79.5±27.87

Table 4: Comparison of serum ALP, GGT and LAP levels of control group Vs. icteric and non-icteric patients of study group

Enzyme	Comparison	t	P	Significance
ALP	C vs. I	28.33	<0.001	HS
	C vs. NI	8.76	<0.001	HS
	I vs. NI	9.7	<0.001	HS
GGT	C vs. I	18.13	<0.001	HS
	C vs. NI	9.36	<0.001	HS
	I vs. NI	4.40	<0.01	HS
LAP	C vs. I	18.43	<0.001	HS
	C vs. NI	11.52	<0.001	HS
	I vs. NI	3.42	<0.01	HS

Table 5: Statistical analysis of comparison of serum ALP, GGT and LAP levels of control group (C) Vs. icteric (I) and non-icteric (NI) patients of study group

Enzyme	Icteric (n=14)				Non-Icteric (n=16)			
	Normal		Above Normal		Normal		Above Normal	
	No.	% age	No.	% age	No.	% age	No.	% age
ALP	-	-	14	100	7	43.75	9	56.25
GGT	1	7.14	13	92.86	4	25.0	12	75.0
LAP	1	7.14	13	92.86	1	6.25	15	93.75

Table 6: showing frequency of elevation of serum ALP, GGT and LAP in icteric and non-icteric groups

Enzyme	Time	Mean ±SD	Mean change±SD	t	p	Significance
ALP	Before	738.03±439.38	177.73±217.91	1.62	>0.05	NS
	After	560.3±346.4				
GGT	Before	184.76±118.55	50.42±45.15	1.74	>0.05	NS
	After	134.36±87.26				
LAP	Before	93.5±33.4	16.96±17.01	1.94	>0.05	NS
	After	76.53±29.51				

Table 7: Statistical analysis of enzyme levels of study group before and after the treatment (n=26)

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DISCUSSION: The present study was intended to compare the levels of serum enzymes – ALP, GGT and LAP in patients suffering from hepatobiliary carcinoma with the age and gender matched controls, and to note any difference of these enzymes a month after initiation of treatment. Serum ALP levels were found to be a reliable index of metastatic liver disease[9-11]. Monitoring the elevation of ALP levels in patients of colorectal carcinoma may be used as an indicator of subsequent liver metastases[12].On the contrary, another finding showed that serum ALP does not increase significantly in cases of liver metastasis[13].Increase in ALP activity also occurs in bone diseases due to increased activity of osteoblasts[14, 15].

It has been suggested that in the hepatobiliary diseases, there is increased synthesis of ALP by the hepatocytes which results in increased enzyme levels in circulation[14]. Hepatic ALP is normally present on the apical domain (i.e., canalicular) of the hepatocyte plasma membrane and in the luminal domain of bile duct epithelium. In cholestasis, retained bile acids solubilize the hepatocyte plasma membrane and facilitate release of ALP[16-18]. The increase levels of serum GGT result from cholestasis in which the bile acids solubilize the hepatic membrane bound enzyme[19, 20]. It is also suggested that the tumor itself may contribute to raised GGT levels because of the pronounced GGT activity of malignant liver cells[21, 22].

Studies from several authors have shown raised levels of serum GGT in liver metastasis[10, 11]. GGT was increased in most of the patients (70%) of liver metastases[23]. Serum GGT is an important marker for Hepatitis B virus-related combined hepatocellular-cholangiocarcinoma[24]. It is shown that serum GGT is not elevated in bone disorders[25, 26]. Thus measurement of serum GGT helps us to distinguish whether bone or liver is the source of increased levels of serum ALP. Elevation of serum GGT levels is an indicator of aggressive tumor behaviors and a predictor of poor clinical outcomes. It may prove to be a useful biomarker for identifying intrahepatic cholangiocarcinoma (ICC) patients at high risk of early recurrence and unfavorableprognosis[27]. Out of the three enzymes, serum LAP was found to be raised in maximum number of cases (93.3%) followed by GGT and ALP in 83.3% and 73.3% cases respectively. LAP is found to be the most sensitive enzyme in hepatobiliary carcinoma[28].

Abnormal levels of serum LAP were reported in100% of cases of carcinoma pancreas and 93% cases of liver metastasis[29]. LAP is raised in diseases of liver and hepatobiliary duct system and the diseases not involving liver and bile duct system are seldom associated with increased LAP[30]. Increased LAP was due to obstruction of common bile duct by the tumor or liver metastasis or both. Significantly elevated LAP levels were observed in liver metastasis[31, 32]. Arise in serum LAP is detected in patients of hepatobiliary pancreatic carcinoma[28]. LAP was found to be elevated in papillary adenocarcinoma of bile duct[33] and in cholestatic liver disease[34].Non-significant elevations of LAP was observed in cases of carcinoma gallbladder without liver metastasis[35]. Serum LAP is not significantly elevated in malignant liver disease as compared to benign liver disease[36]. Patients with liver metastasis of non-pancreatic origin and without jaundice had increased LAP levels suggesting that hepatic infiltration is the cause of rise in liver metastasis[29].

Cholestatic liver diseases are characterized by impaired hepatocellular secretion of bile, resulting in intracellular accumulation of bile acids which result in a shift in the oxidant/prooxidant balance in favor of increased free radical activity and injury of different tissues[37].It is concluded that rise in LAP seen in both icteric and non-icteric groups was due to hepatocellular dysfunction. Whereas ALP and GGT showed greater rise in icteric group as compared to non-icteric group indicating that hepatic dysfunction with jaundice was the cause of elevated levels, LAP rises with

hepatic dysfunction irrespective of jaundice, it is a better indicator of hepatobiliary malignancy[28]. Lowering of LAP levels was either due to removal of primary tumor or suppression of primary tumor with subsequent decrease in size of secondaries by various modes of treatment (surgery, radiotherapy or chemotherapy).

Fall in levels were not statistically significant because the residual tumor still remained in the body. Moreover these estimations were done when patients were still taking the treatment in the form of radiotherapy or chemotherapy and high levels may have not disappeared from the circulation. These patients may have shown fall in the levels after completion of treatment.

CONCLUSIONS: All the three enzymes i.e. ALP, GGT and LAP are significantly elevated in the patients with hepatobiliary carcinoma and the elevations are significantly higher in icteric patients as compared to nonicteric patients. Out of these enzymes, LAP is the most sensitive in diagnosis of hepatobiliary carcinoma. It is more useful in the screening of non-icteric cases of hepatobiliary carcinoma as it rises more frequently in non-icteric cases. Thus serum LAP is a better indicator of hepatobiliary carcinoma. Monitoring LAP is a simple, low cost, and relatively sensitive screening tool for detecting hepatobiliary carcinoma.

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