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# ROLE OF ACUTE PHASE PROTEINS STATUS IN CHRONIC ALCOHOLIC LIVER DISEASES

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**ABSTRACT:**

**Back ground**: Alcoholic cirrhosis is a condition of irreversible liver disease due to the chronic inflammatory and toxic effects of ethanol on the liver. Acute alcoholic hepatitis occurs in habitual drinkers, often a period of increased alcohol intake. Although, the clinical features may mimic acute viral hepatitis. Progression of liver fibrosis to cirrhosis is dangerous as well as potentially life-threatening condition that occurs when inflammation and scarring damage. Several biochemical parameters are altered in this condition .A combination of tests are useful for diagnosis of cirrhosis.

**Aim & objective**: The aim of the study evaluates the possible association between the acute phase proteins along with other biochemical parameters in alcoholic liver disease.

Materials and methods: A total 30 chronic alcoholic liver disease patients between the ages of 32 and 60 years are selected for the study group, 30 healthy age matched healthy individuals are selected as a control group. All the parameters are analyzed by conventional standardized methods and compared between the two groups.

**Results**: The mean levels of acute phase proteins Transferrin, alpha 1 antitrypsin are significantly decreased. CRP and sialic acid levels are significantly increased chronic alcoholic liver disease patients.

**Conclusion**: Evaluation of plasma acute phase proteins (transferrin, alpha 1 antitrypsin, CRP) & sialic acid are potentially useful diagnostic markers for the assessment of chronic alcoholic liver disease along with other biochemical parameters.

**INTRODUCTION:** Alcohol consumption is well entrenched in the social fabric of many adult populations, virtually constituting a behavioral norm. It is legal, readily available and cheap.

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Sustained excessive alcohol consumption is a brain-centered addictive behavioral disorder that crosses all boundaries of gender, race, age, economic strata and, in many patients, might lead to alcoholic liver disease (ALD) [1–3].

Heavy drinking significantly increases morbidity and mortality from infectious diseases [4] and the risk of cardiovascular, brain, pancreatic, renal, cerebral and oncological diseases.

Alcoholic liver disease represents a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis) [3]. Furthermore, sustained excessive alcohol intake favors the progression of other liver diseases, such as virus-related, chronic hepatitis, also increasing the risk of hepatocellular carcinoma [5–7].

Generally serum proteins albumin and globulin are measured to assess liver function. Values for total serum proteins range from 6 to 8 g/dl. Of this total, between 52 and 68% (3.5-5g/dl) is albumin; the remainder are globulins and fibrinogen. A low serum albumin indicates poor liver function. Decreased serum albumin levels are not seen in acute liver failure cases because it takes several weeks to decrease [8]. The most common reason for a low albumin levels in chronic liver failure cases due to cirrhosis.

The serum albumin concentration is usually normal in chronic liver disease until cirrhosis and significant liver damage has occurred. In advanced liver disease, the serum albumin level may be less than 3.5 g/dl. Albumin levels can be low in conditions other than liver disease, such as severe malnutrition and some kidney diseases that cause extensive protein wasting [9].

Though ALD group shows significant increase in globulin level in comparison to control group, the albumin level was found to be significantly decreased in study group (ALD) when compared with control group. In ALD group hypoalbuminemia was observed. Common features of chronic alcoholic liver disease are progressive hypoalbuminemia [10, 11]. Acute exposure to alcohol depressed albumin. The decrease in serum albumin level is attributed to nutritional status of the subjects [10, 12].

On the other hand, the albumin is a potential subject of formation of adduct by acetaldehyde, an alcohol metabolite. This albumin or other protein adducts can stimulate the formation of immunoglobulins, thus causing a rise in serum globulin level [10, 13].

In the present study, significant decrease in total protein was observed in study group when compared with normal healthy control group. Ethanol consumption slows down the rate of hepatic protein catabolism [14].

The aminotransferases (transaminases) are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases such as hepatitis. They include the aspartate amino transferase (AST) and the alanine aminotransferase (ALT). AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration. ALT is found primarily in the liver. The aminotransferases are normally present in the serum in low concentrations. These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane resulting in increased permeability. Thus, the absolute elevations of the aminotransferases are significant markers for acute hepatocellular disorders.

The pattern of the aminotransferase elevation can be helpful diagnostically. In most acute hepatocellular disorders, the ALT is higher than or equal to the AST. But in the alcoholic liver disease cases AST significantly increased than compared ALT. The AST in alcoholic liver disease is rarely >300 U/L and the ALT is often normal. A low level of ALT in the serum is due to an alcohol-induced deficiency of pyridoxalphosphate [15, 16].

Elevation of liver-derived alkaline phosphatase (ALP) is not totally specific for cholestasis, and a less than threefold elevation can be seen in almost any type of liver disease. Alkaline phosphatase elevations greater than four times normal occur primarily in patients with cholestatic liver disorders, infiltrative liver diseases such as cancer and amyloidosis, and bone conditions characterized by rapid bone turnover (e.g., Paget's disease).

In bone diseases, the elevation is due to increased levels of the bone isoenzymes. In liver diseases, the elevation is almost always due to increased amounts of the liver isoenzyme [17]. Gamma-glutamyltransferase (GGT) is the most widely used laboratory marker of alcoholism and heavy drinking.

However, the specificity of increased serum GGT limits its use for general screening purposes. Its value in the follow-up of various treatment programs, however, is well established [18-20].

We consider it probable that pre-existing liver disease affects the response to ethanol, so that greater amounts of GGT are released from hepatic tissue; alternatively, drinkers may have a higher GGT activity in this tissue as a result of enzyme induction by ethanol. The alcohol challenge test was an effective discriminator between moderate drinkers and abstainers [21].

Sialic acid (SA) is the name for a series of acyl-derivatives of neuraminic acids that occur as non-reducing terminal residues of glycoproteins or glycolipids in biological fluids and cell membranes. The normal range of total sialic acid (TSA) level in serum/plasma is 1.58 - 2.22 mmol/L [22]. Sialic acid levels were elevated by high alcohol consumption and reduced during abstinence, especially among women. Thus, Sialic acid seems to be an interesting marker that needs further evaluation as a diagnostic tool for alcohol abuse [23-27].

Acute phase proteins, transferrinis the major circulating iron binding protein and correlates with total iron binding capacity of plasma. It is also synthesized by liver and has short half-life. Transferrin is glycoprotein containing up to nine terminal sialic acid residues. In healthy individuals the trisialo, tetrasialo and pentasialo forms predominate. (Abnormalities of the glycosylation of transferrin occur in the congenital disorders of glycosylation and in chronic alcohol abuse.)

Alcohol consumption inhibits glycation of several glycoproteins, including transferrin, in alcoholics plasma transferrin often lacks up to four of these sialic acid residues resulting in asialo –and disialotransferrins, collectively termed carbohydrate deficient transferrin (CDT). CDT measurement has been proposed as a marker of excessive alcohol consumption [28, 29].

C-reactive protein (CRP) is a plasma protein which is synthesized in the hepatocyte and the levels of CRP increased in parallel with the progression of chronic liver diseases &inflammatory states [30, 31].

Alpha-2-macroglobulin (A2M) is a proteinase inhibitor. Inflammatory states usually increase synthesis of many plasma proteins, acute phase response, including CRP, but decrease the albumin level [32]. Cells synthesizing A2M are in first-order hepatocytes and in second-order activated into cells [33-35], levels of alpha 2-MG, alpha 1-acid glycoprotein & hepatoglobin were lower in alcoholic cirrhosis [36, 37].

The chronic alcohol increases the risk of hyperuricaemia because it interferes with the removal of uric acid from the body. Decreases the capacity of kidney to excrete uric acid; it leads to increased uric acid levels accumulation in the blood [38].

**MATERIALS AND METHODS:** Thirty alcoholic patients, between the ages of 32 and 60 years and with adequate information on clinical and laboratory variables were included retrospectively. The duration of this study was from Nov-2012 to Apirl- 2013 who underwent treatment in Shridevi Institute of Medical Sciences and Research Hospital, Tumkur, were included after taking the inform consent from the patients and the study was approved by the institutional ethical committee overseeing human studies. Thirty healthy, age, and sex matched subjects were selected as controls. Experiments were done in accordance with the Helsinki Declaration of 1975.

Patients with any parenteral drug use or long term medication (e.g. Phenothiazines, antidiabetics, anti-tuberculars, antiepileptics and antibiotics) were excluded. Patients with history suggestive of infective hepatitis in the past were also excluded from analysis. The controls chosen for the study were nonalcoholic healthy individuals of similar age group without liver disease, obesity and any other inflammatory disease. Patients suffering from disease of any origin other than alcohol intake were excluded from the study. This information has been collected during the inpatient assessment with detailed interviews.

Peripheral venous blood samples were collected in an early morning fasting state, within 72 hours of the last dose of alcohol. The blood samples were centrifuged at 2000×g for 10 min.

After extracting the serum sample, biochemical analysis was carried out for levels of all parameters (serum total bilirubin, SGOT, SGPT, ALP &GGT, Plasma proteins, sialic acid &NPN Substances were done using conventional standardized methods. on ERBA Chem – 5V2 semi auto analyzer & Cistronic digital calorimeter with diagnostic kits from Erba. alpha-1-antitrypsin, CRP & Transferrin are analyzed by ELISA method.

**Statistical analysis:** The statistical analysis was carried out by using the SPSS (Statistical Package for Social Sciences) software. The Student't' test was applied for the statistical analysis and the results were expressed in mean ± SD, P values ($p < 0.001$) were considered as highly significant.

**RESULTS & DISCUSSION:** The present study represents the various biochemical parameters and its relation between the control healthy group and chronic liver disease group. Serum mean total bilirubin 7.96 ± 3.141mg/dl, conjugated bilirubin 3.604 ± 1.39mg/dl & unconjugated bilirubin 4.284 ± 1.802mg/dl was observed in ALD cases when compared with controls mean serum total bilirubin 0.868 ± 0.184mg/dl, serum conjugated bilirubin 0.26 ± 0.057 mg/dl & unconjugated bilirubin 0.708 ± 0.138mg/dl the mean difference was statistically significant.

Conjugated hyperbilirubinemia implied liver or biliary tract disease. Since the rate limiting step in bilirubin metabolism is not conjugation of bilirubin, rather transport of bilirubin into bile canaliculi. Thus elevation of conjugated fraction was seen in cirrhosis patients in comparison to controls.

In patients included in the study with the mean serum total protein (5.478 ± 0.59 gm/dl) & serum albumin (2.468 ± 0.416 gm/dl) level was decreased in study group & when compared with controls serum total protein (6.97 ± 0.49 gm/dl) &serum albumin (3.676 ± 0.198gm/dl).

The mean globulin levels in the study group was increased (3.082± 0.184gm/dl) and the controls was decreased (2.852 ± 0.387gm/dl) the mean difference was statistically significant. The observed hypoalbuminemia in the study group reflects severe liver damage and decreased albumin synthesis. Hypoalbuminemia was observed in chronic alcoholic liver disease patients in comparison to controls (**Table 1**).

In the chronic alcoholic liver disease patients, mean serum AST & ALT levels 170 ± 13.9 IU/L & 118.8 ± 26.21 IU/L were increased when compared with controls (23.56 ± 4.204 IU/L and 28.91± 4.405 IU/L). These enzymes are released into the blood due to damage of liver cell membrane resulting in increased permeability. The present study collaborate the previous related studies.

Increased mean levels of serum alkaline phosphatases (134.9 ± 23.33 IU/L were observed when compared with controls (92 ± 17.57 IU/L), may be suggestive of intrahepatic cholestasis due to oedema of inflamed hepatocytes.

The significant difference of GGT values are observed between the study groups compared to control group (31.8 ± 4.064 IU/L vs 56.8 ± 6.783 IU/L)

The characteristic of the patients showed, the mean level Transferrin in serum is significantly decreased (234± 9.81 vs 175 ± 12.6 mg/dl), alpha-1-antitrypsin was significantly decreased (185.5 ± 34.07 mg/dl vs 132 ± 19.07 mg/dl) & CRP levels was significantly elevated in study group (1.2 ± 0.47 mg/L vs 3.93 ± 0.588 mg/L ).

The total Sialic acid in control group is 57.33± 13.18 mg /dl, while in alcoholic patients the mean total sialic acid levels was 81.24± 7.07mg/dl (table 2). The serum SA level in alcoholics was significantly increased. The elevations of sialic acid content in our patients suggest that consequence of liver damage resulting in abnormal carbohydrate composition of the fibrinogen in the disease progression. Fibrinogen contains 0.6 % sialic acid. Fibrinogen and sialic acid are both acute phase reactants. Kaniak *et al* [39] have studied sialic acid contents of the glycoproteins and seromucoid in viral hepatitis, liver cirrhosis, inflammations of the biliary tract and malignant neoplasms of liver. Matsuzaki et al [40] have also reported variations in serum sialic acid level in liver cirrhosis, the determination of sialic acid can be clinically useful for the diagnosis of cirrhosis and liver cancer.

In **table 2**, chronic alcoholic liver disease group shows significantly higher uric acid value (7.963 ± 1.337) when compared with control group (4.19 ± 0.5442). There is no significant difference of urea levels are observed between the groups (29.6± 6.95 Vs. 23.2 ± 5.143). Though the increased creatinine levels are observed in alcoholic liver disease group(1.2 ± 0.160) and statistically significant change was observed in alcoholic liver disease groups when compared with normal healthy persons (0.58 ± 0.179). Therefore, the bilirubin level in association with urea, creatinine, and uric acid may be useful as markers for ALD.

**TABLE 1: MEAN ± S.D OF VARIOUS LIVER FUNCTIONAL TESTS IN NONALCOHOLIC HEALTHY INDIVIDUALS (CONTROLS) & ALCOHOLICS (STUDY) GROUPS**

| PARAMETERS | Control Group Mean ± S.D | Study Group Mean ± S.D | P –value |
|---|---|---|---|
| Total Bilirubin (mg/dl) | 0.868 ± 0.184 | 7.96 ± 3.141 | < 0.001 |
| Conjugated Bilirubin(mg/dl) | 0.26 ± 0.057 | 3.604 ± 1.39 | < 0.001 |
| Unconjugated Bilirubin (mg/dl) | 0.708 ± 0.138 | 4.284 ± 1.802 | < 0.001 |
| Total Proteins (gm/dl) | 6.97 ± 0.49 | 5.478 ± 0.59 | < 0.001 |
| Albumin (gm/dl) | 3.676± 0.198 | 2.468 ± 0.416 | < 0.001 |
| Globulin (gm/dl) | 2.852 ± 0.387 | 3.082 ± 0.184 | < 0.001 |
| A/G ratio | 1.244 ± 0.100 | 1.156 ± 0.249 | < 0.107 |
| AST (IU/L) | 23.56 ± 4.204 | 170 ± 13.9 | < 0.001 |
| ALT (IU/L) | 28.91 ± 4.405 | 118.8 ± 26.21 | < 0.001 |
| ALP (IU/L) | 92 ± 17.57 | 134.9 ± 23.33 | < 0.001 |
| GGT (IU/L) | 31.8 ± 4.064 | 56.8 ± 6.783 | < 0.001 |

**TABLE 2: MEAN ± S.D OF ACUTE PHASE PROTEINS, SIALIC ACID & NPN SUBSTANCES IN NON-ALCOHOLIC HEALTHY INDIVIDUALS (CONTROL) & ALCOHOLICS (STUDY) GROUPS**

| PARAMETERS | Control Group Mean ± SD | Study Group Mean ± SD | P –value |
|---|---|---|---|
| Transferrin (mg/dl) | 234± 9.81 | 175± 12.6 | < 0.001 |
| CRP (mg/L) | 1.2 ± 0.47 | 3.93 ± 0.588 | < 0.002 |
| alpha-1-antitrypsin (mg/dl) | 185.5 ± 34.07 | 132 ± 19.07 | < 0.001 |
| Serum Sialic acid (mg/dl) | 57.33 ± 13.18 | 81.24 ± 7.07 | < 0.001 |
| Urea | 29.6±6.95 | 23.2± 5.143 | < 0.007 |
| Uric acid | 4.19 ± 0.5442 | 7.963 ± 1.337 | < 0.001 |
| Creatinine | 0.58 ± 0.179 | 1.2± 0.160 | < 0.005 |

**CONCLUSION:** In the early stages of cirrhosis termed compensated cirrhosis, there may be no signs and symptoms of liver damage. As cirrhosis progresses, decompensation occurs and mortality and morbidity are increased. In the present study, we have analyzed various biochemical parameters in alcoholic liver disease patients as well as controls.

It is concluded that variation of plasma acute phase proteins (Transferrin, alpha-1-antitripsin, CRP) & sialic acid levels in alcoholic liver disease patients is an important diagnostic tool in addition to its value in prognosis. Patients undergoing treatment for cirrhosis liver may benefit more in future from this noninvasive test.

Further investigations into the nature of alterations in the sialic acid & acute phase proteins content of plasma glycoproteins may provide a basis for better understanding of pathogenesis and mechanism responsible for it in the patients of liver cirrhosis.

Evaluation of bio-chemical parameters not only predicts the decompensating but also increases the scope of early diagnosis, prognosis, and therapy there by reducing the mortality and morbidity of cirrhosis.

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