

Liver enzyme alterations in hepatic diseases: Clinical insights into ALT, AST, and ALP Variations

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Abstract

Liver enzymes such as ALT, AST, and ALP are critical biomarkers used to assess liver function, diagnose, and treat hepatic diseases. These enzymes reflect hepatocyte integrity and can indicate the incidence and severity of liver conditions.

Objective: This study aimed to evaluate and compare serum levels of ALT, AST, and ALP across various liver diseases, including Hepatitis B, alcoholic hepatitis, autoimmune hepatitis (AIH), obstructive jaundice, and Hepatitis C (HCV). The study also assessed gender differences in liver enzyme levels and investigated changes in serum TNF α protein levels in Hepatitis B patients via western blot.

Methods: Serum enzyme levels were measured in blood samples from patients grouped by acute and chronic Hepatitis B, Alcoholic Hepatitis, Obstructive Jaundice, Autoimmune hepatitis, and hepatitis C virus patient. A control group of healthy individuals was included for statistical comparison. Western blot analysis was performed to observe the TNF α protein levels in Hepatitis B patients.

Results: Results showed no significant difference in baseline ALT, AST, and ALP levels between healthy men and women. However, a significant increase in TNF α protein was observed in both male and female Hepatitis B patients compared to controls. Significant differences in ALT, AST, and ALP levels were found between acute and chronic Hepatitis B patients ($p<0.001$). Both male and female patients exhibited significant differences ($p<0.001$) in these enzyme levels when compared to the controls across the various liver pathologies.

Conclusion: This investigation provides insight into the specific alterations in ALT, AST, and ALP levels across different liver diseases, offering potential diagnostic and monitoring markers for clinical practice.

Keywords: Liver Enzymes; Hepatic Disease; ALT; AST ALP; Hepatitis B; Hepatitis C.

1. Introduction

The liver is a vital complex organ that performs pivotal role in nutrient metabolism, glucose homeostasis, and detoxification via amino acid deamination [1, 2]. Acting alongside spleen, it recycles blood cells and synthesizes lipoproteins, bile and plasma proteins [2]. In case of hepatic dysfunction, biochemical abnormalities are reflected through liver function tests [3]. These tests measure the serum levels of liver enzymes, particularly alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), as they usually reflect hepatocyte integrity [4]. The detection of abnormal levels of these key enzymes is often the first indication of the

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presence of liver disease or hepatic injury. A change of normal test values can help determine the area of hepatic injury, and the elevation pattern can help organize a differential diagnosis. Among these tests, ALT, previously called serum glutamate-pyruvate aminotransferase [SGPT], measures an enzyme produced in hepatocytes, which is a key biomarker of hepatocellular injury and is more specific than AST [5]. AST, previously called serum glutamate-oxaloacetate aminotransferase [SGOT], is a hepatic mitochondrial isoenzyme that responds to liver and cellular stresses in a similar way to ALT [6]. Finally, ALP, a member of a family of zinc metalloprotein enzymes, is made in the cells lining bile ducts and canaliculi and is released following accumulation of bile salts or cholestasis[7]. Therefore, based on these enzymes, the origin and severity of liver disease is best assessed.

These enzymes are drastically impacted by multiple liver disease states. Among these alcoholic hepatitis manifests after prolonged (usually >12 months) heavy drinking[8]. Biochemically, patients exhibit raised bilirubin (>3 mg/ dL), along with elevation of aspartate AST (>50 IU/mL) and ALT (>300–400 U/L)[8]. As alcoholic hepatitis represents most acute and severe manifestation of alcohol-associated liver disease, liver enzymes play a key role in its diagnosis and management [9]. Similarly, autoimmune hepatitis (AIH) is an inflammatory liver disease, affecting mainly females, characterized by elevated liver enzymes[10]. The laboratory biochemical profile of AIH shows aminotransferases concentrations ranging up to >50 times the normal levels with exceptions on ALP levels [11]. Further, in obstructive jaundice, pattern of liver enzymes particularly ALP dictates the clinical outcomes [12]. In hepatitis C, liver enzymes determine stages of disease as well as prognosis, for example, AST/ALT ratio > 1 suggests cirrhosis and excessive liver damage [13, 14]. Although liver enzymes are commonly ordered tests, yet, there remains a variation in data for abnormalities in liver enzymes across various disease models. Data based knowledgeable assessment of liver enzymes is required to fully understand their pathophysiology. The best knowledge and interpretation of data can be achieved by combining known data with novel clinical research studies. As a pattern of biochemical abnormalities can provide vital clues to the etiology and treatment of hepatic pathologies, therefore, their updated assessment is vital clinical pursuit. Therefore, the overall aim of this study was to obtain liver enzyme analysis, particularly AST, ALP, and ALT in blood samples of patients suffering from various liver diseases.

2. Materials and Methods

2.1. Research subjects

Both the subjects and the Tripoli Medical Center provided written consent. Ethical review board approval was obtained before conducting the study.

This study was carried out on a total of 62 adult patients diagnosed with one of these liver diseases acute hepatitis B (n= 9) and chronic hepatitis B (n=9), alcoholic hepatitis(n=5), Autoimmune Hepatitis(n=5), Obstructive Jaundice (n=5), and Hepatitis C virus(n=9). The normal healthy individuals (n=20) were participated as control group. The diagnoses were confirmed through a combination of biochemical, radiological, and microbiological assessments and clinical diagnosis by specialists in the liver disease department.

The data of study collected in the period from December 2019 to October 2023 Tripoli city- Libya. Face-to-face interviews were carried out using a questioner who inquired about each patient's name, age, gender, duration of disease, and family history. Individuals with other diseases, those taking any medication that affects serum ALT, AST, and ALP levels, pregnant women, and those with a family history of liver disorders are excluded from the study.

2.2. Blood Collection

Blood samples for serum ALT, AST and ALP were obtained with 21G needle mounted on 5 ml syringe. The blood samples were placed in regular sample bottles and centrifuged at 3000 rpm, 4 °C, for 10 minutes to separate sera.

2.3. Liver function biomarkers assay.

To detect liver biomarkers, an Olympus AU600 multifunctional analyzer was used, and its procedures were carried out according to manufacturer's guidelines (Tokyo, Japan). The levels of ALT, AST and ALP enzyme activity were measured in units of liters (U/L). The absorbance of reaction was determined at 546 nm.

2.4. Western blots

Proteins were extracted from as described in an earlier report [15]. The lysates were spun down at 20,000 × g to pellet genomic DNA and cellular debris, and the supernatant was aliquoted into fresh, low-protein-binding tubes. Samples were stored at -80 °C until further use. For WB, protein extracts were mixed 3:1 with 4 × Laemmli buffer (Biorad, cat.

no. 1610747) containing β -mercaptoethanol and heated at 95 °C for 10 min. For primary antibody details, TNF α antibody was obtained from Abcam (ab183218). Secondary antibody (ab150077) were diluted 1:10,000 in blocking buffer containing 0.1% Tween-20 and 0.01% SDS. Membranes were imaged dry on an Odyssey CLx scanner (LI-COR Biosciences), and blot images were visualised and quantified in the Image Studio software (version 5.2.5; LI-COR Biosciences).

2.5. Statistical Analysis

Statistical analyses were performed using GraphPad software and data were expressed as mean and standard deviation for continuous variables, and as median and range for categorical variables. T-test and ANOVA analysis was used to evaluate the relationships between liver enzymes and other parameters such as gender and disease state.

3. Results and Discussion

3.1. Measurement of enzyme levels in healthy individuals

We first measured the serum levels of classical liver enzymes in healthy male and female to assess the baseline levels of liver homeostasis. Our results showed that there was no significant difference in the amount of the liver enzymes at baseline healthy men and women (Figure 1 A-C). Among alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), there was no significant difference in serum levels of ALT (Figure 1 A), AST (Figure 1 B), and ALP (Figure 1 C); between healthy men and women (Figure 1). As these tests are the most common laboratory tests used for the detection of liver diseases, they serve as a biological marker of liver health. The liver aminotransferases (ALT and AST) are found copiously within liver, and they catalyze the transfer of amino groups to generate products in gluconeogenesis and amino acid metabolism [16]. Similarly, alkaline phosphatase catalyzes the hydrolysis of inorganic pyrophosphate, which is a vascular calcification inhibitor and serves as a marker of liver or bone disease [17, 18]. Overall, our results showed that healthy male and female individuals had similar levels of liver enzymes indicating a healthy baseline for our further studies.

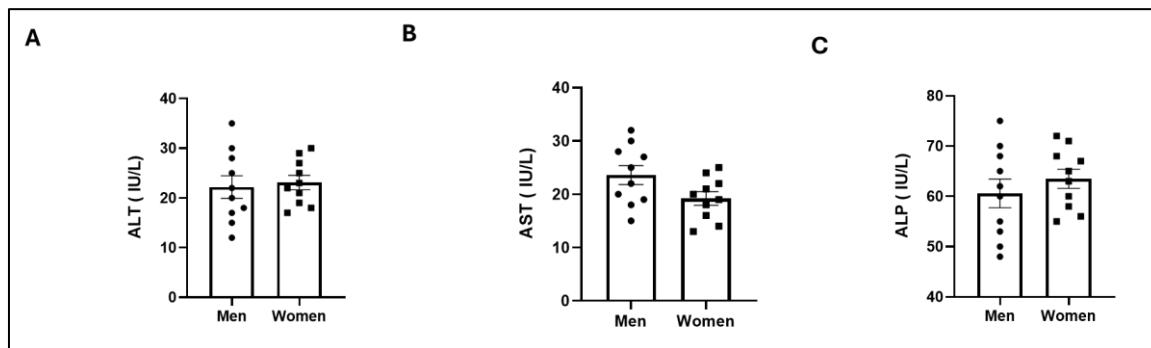


Figure 1 Measurement of baseline liver enzymes and their comparison between men and women. The serum samples were collected from the healthy male and female individuals and compared to assess the levels of ALT (IU/mL), AST (IU/mL), and ALP (IU/mL)

3.2. TNF α levels in serum samples of healthy and HepB patients

Next, collected the whole blood sample and performed the western blot as indicated in the methodology. Our results showed that there was significant difference in the protein levels of TNF α in both men and women, when compared between healthy and HepB patients (Figure 1). Among males, the protein levels of TNF α increased in samples of HepB patients, indicating loss of cell structure, inflammation and apoptosis (Figure 1A). Similar observations were made in female samples as well which showed a spike in serum protein levels of TNF α (Figure 1B). Overall, higher serum levels of TNF α exhibited a systemic inflammatory process in liver patients, and a possible exacerbation of their negative clinical outcomes. In the liver, TNF α mediates hepatocellular death and is implicated in inflammation, viral hepatitis, and liver cancer [19]. These pathophysiological properties of TNF α make it necessary to study other inflammatory liver markers and identify the most relevant targets for therapeutic intervention. It is now evident that TNF α inflammation is closely related to elevated serum levels of liver enzymes in a large number of cases [19, 20]. Therefore, based on these results, it is vital to confirm the elevation and/or altered status of enzyme levels in various liver diseases.

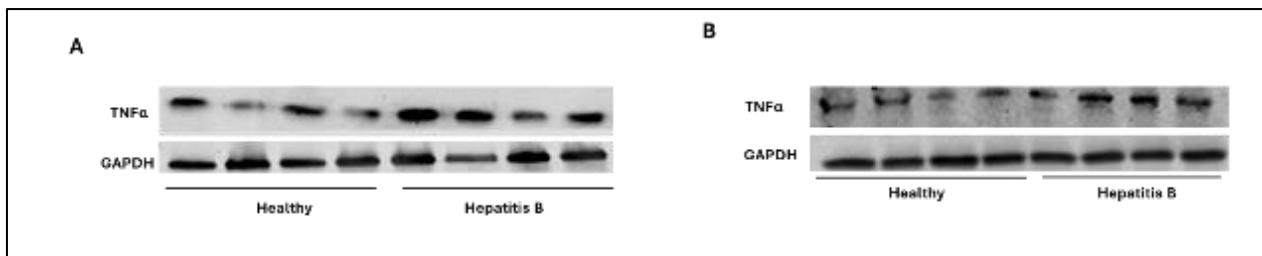


Figure 2 Results showing the protein abundance of TNF α in serum of (A) healthy men and (B) women and their HepB counterparts

3.3. Levels of liver enzymes in serum samples of HepB patients

We next analyzed changes in liver enzymes in Hep B patients i.e. in both acute and chronic patients to establish the hypothesis that these enzymes are altered and vary between both the genders. Our results showed that there was significant difference in serum levels of ALT ($p<0.001$) (Figure 3 A), AST ($p<0.001$) (Figure 3 B), and ALP ($p<0.001$) (Figure 3 C); between acute and chronic Hep B patients (Figure 3). Normal serum ALT is 7–56 IU/ L and HepB can significantly increases ALT levels. Also, viral hepatitis like B are responsible for a marked increase in aminotransferase levels [21]. Likewise, an increase in AST levels of acute HepB patients highlights higher liver inflammation and damage. As AST is found in mitochondria, marked increase in its serum levels indicates increasing damage related to oxidative homeostasis [17, 21]. ALP is primarily found in the hepatobiliary tract and bone and is involved in multiple dephosphorylating reactions. As our findings are above the normal range for ALP (30-120 IU/L), this indicates both liver damage and increased osteoblastic activity, which can subsequently trigger osteoclast activation [22].

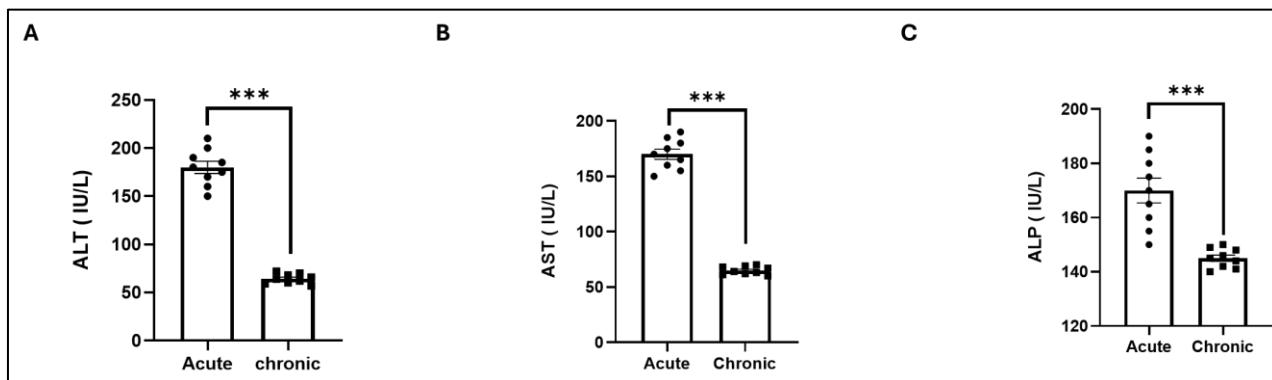


Figure 3 Measurement of baseline liver enzymes and their comparison between acute and chronic HepB patients. The serum samples were collected from the acute and chronic HepB patients and compared to assess the levels of ALT (IU/mL), AST (IU/mL), and ALP (IU/mL)

3.4. Levels of liver enzymes in serum samples of Alcoholic Hepatitis patients

Next, we compared the levels of various liver enzymes between healthy individuals and alcoholic hepatitis patients (Figure 4). Our results showed that in males (Figure 4A), there was significant difference ($p<0.001$) in serum enzyme levels of ALT, AST, and ALP in control and alcoholic hepatitis patients. Likewise, similar results were obtained in female patients where significant difference ($p<0.001$) was observed in serum enzyme levels of ALT, AST, and ALP in control and alcoholic hepatitis patients. As alcoholic hepatitis is characterized by a rapid of liver-related complications in patients with excessive alcohol use, and it has a high short-term mortality[23]. Current clinical guidelines indicate that Common laboratory findings include elevated AST and alanine aminotransferase ALT (rarely exceeding 400 IU/mL), and an AST/ALT ratio >2 . Our findings were in line with these findings and showed that strong increase in ALP. However, the AST/ALT ratio >2 was not observed in our results[23]. Also, alcoholic hepatitis is closely related to surge of multiple inflammatory cytokines, particularly TNF α [24]. These reports are in line with our findings on serum TNF α as well (Figure 2).

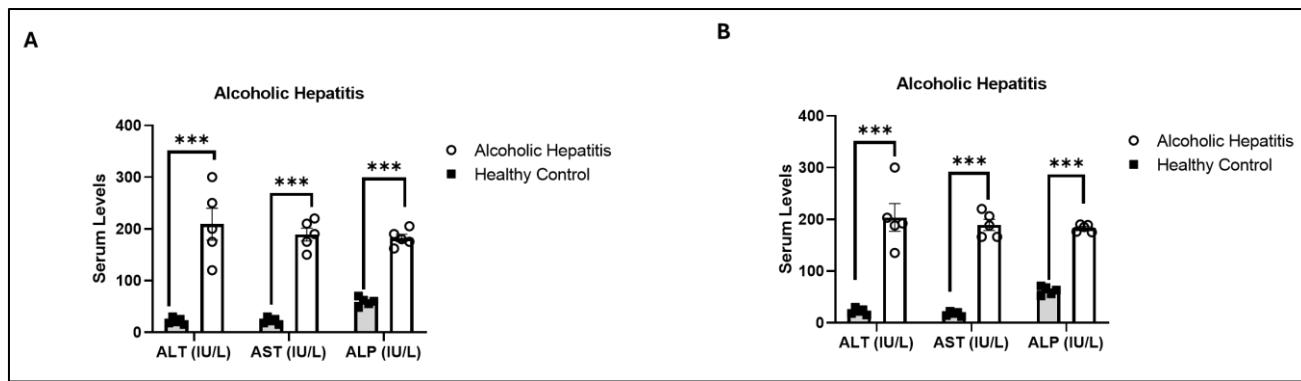


Figure 4 Measurement of liver enzymes and their comparison between (A) men and (B) women in alcoholic hepatitis. The serum samples were collected from the healthy male and female individuals and compared to patients of alcoholic hepatitis to assess the levels of ALT (IU/mL), AST (IU/mL), and ALP (IU/mL)

3.5. Levels of liver enzymes in serum samples of Autoimmune Hepatitis patients

Next, we compared the levels of ALT, AST, and ALP enzymes between healthy individuals and autoimmune hepatitis patients (Figure 5). Our results showed that between male participants (Figure 5A), there was significant difference ($p<0.001$) in serum enzyme levels of ALT, AST, and ALP in control and AIH patient groups. Likewise, similar results were obtained in female patients where significant difference ($p<0.01$) was observed in serum enzyme levels of ALT, AST, and ALP ($p<0.001$) in control and AIH patients. AIH is hepatic disorder with a female predilection and causes jaundice and cirrhosis in a majority of patients [25]. AIH elevates bilirubin, ALP, and gamma globulins in autoimmune hepatitis[26]. A disproportionate elevation of ALP is usually observed in female patients and prompts consideration of other differentials such as primary biliary cholangitis [27]. Interestingly, our results confirmed these findings as we observed a female predilection in ALP levels *in vivo* (Figure 5B). Furthermore, literature suggests that patients with higher elevations in aminotransferases had a better prognosis, thus favoring male subjects as per our findings [28].

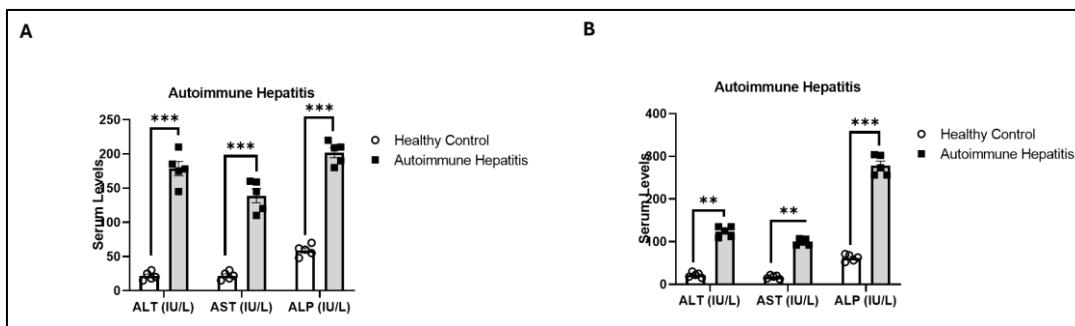


Figure 5 Measurement of liver enzymes and their comparison between (A) men and (B) women in autoimmune hepatitis. The serum samples were collected from the healthy male and female individuals and compared to patients of AIH to assess the levels of ALT (IU/mL), AST (IU/mL), and ALP (IU/mL)

3.6. Levels of liver enzymes in serum samples of Obstructive Jaundice patients

Following the previous line of research, we compared the levels of ALT, AST, and ALP enzymes between healthy individuals and obstructive jaundice patients (Figure 6). Our results showed that between male participants (Figure 6A), there was significant difference ($p<0.01$) in serum enzyme levels of ALT, AST, and ALP ($p<0.001$) in control and obstructive jaundice patient groups. Likewise, similar results were obtained in female patients where significant difference ($p<0.01$) was observed in serum enzyme levels of ALT, AST, and ALP ($p<0.001$) in control and obstructive jaundice patients. It is vital to note that ALP levels played were highest in both cases, indicating its importance in obstructive jaundice patients. Classically, in jaundice, skin or sclera of the eyes become yellow, and is a unique and distinct sign of the hepatobiliary diseases [29]. In obstructive jaundice, tempered free flow of bile from the liver to the gall bladder and then to the small intestine results in complications such as endotoxemia, apoptosis, highly elevated liver enzymes and abdominal pain [29, 30]. As complications of jaundice include sepsis, pancreatitis, renal and liver failure, therefore understanding of liver enzymes and their clinical outcomes play an important role in clinical success and prognosis.

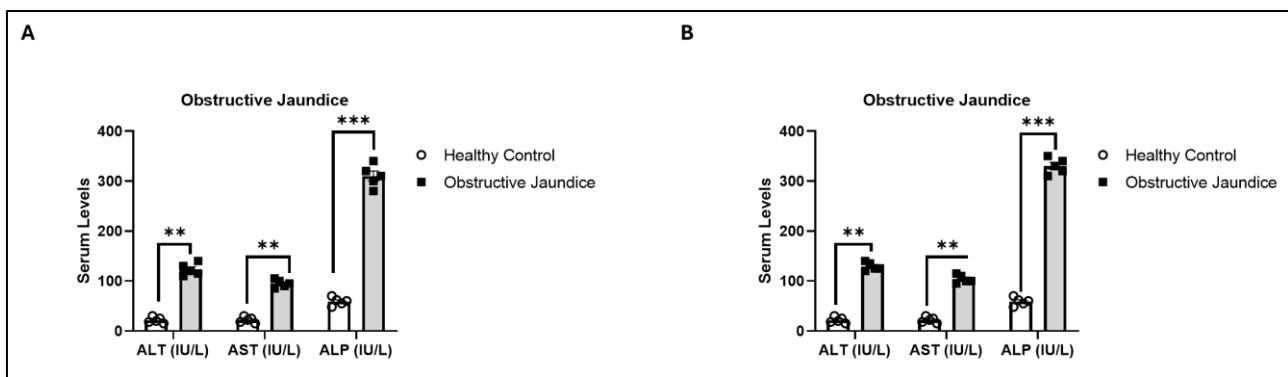


Figure 6 Measurement of liver enzymes and their comparison between (A) men and (B) women in obstructive jaundice. The serum samples were collected from the healthy male and female individuals and compared to patients of obstructive jaundice patients to assess the levels of ALT (IU/mL), AST (IU/mL), and ALP (IU/mL)

3.7. Levels of liver enzymes in serum samples of Hepatitis C patients

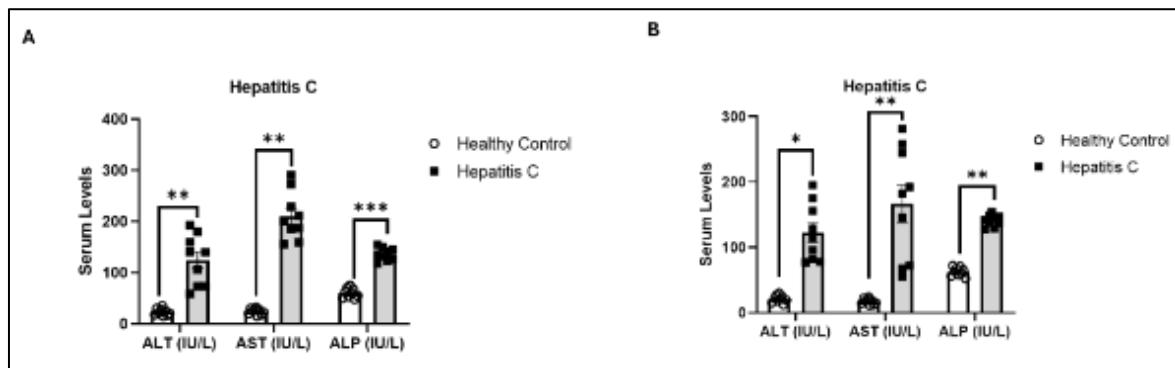


Figure 7 Measurement of liver enzymes and their comparison between (A) men and (B) women in HCV patients. The serum samples were collected from the healthy male and female individuals and compared to patients of HCV patients to assess the levels of ALT (IU/mL), AST (IU/mL), and ALP (IU/mL)

Finally, we compared the levels of ALT, AST, and ALP enzymes between healthy individuals and Hepatitis C (HCV) patients (Figure 7). Our results showed that between male participants (Figure 7A), there was significant difference ($p<0.01$) in serum enzyme levels of ALT, AST, and ALP ($p<0.01$) in control and HCV patient groups. Likewise, similar results were obtained in female patients where significant difference ($p<0.05$) was observed in serum enzyme levels of ALT, AST, ($p<0.01$) and ALP ($p<0.01$) in control and HCV patients. A recent study showed that Although HCV patients had higher ALP levels, the mean levels were within normal limit [31]. However, our findings contrasted with this study [31], as we observed higher levels of ALP compared to the control group (Figure 7). Another report stated that in a patient with high serum HCV viral load (HCV-RNA 17,000,000 IU/ml) there was no significant increase in liver enzymes [32]. Yet, our results are in agreement with EASL recommendations on treatment of hepatitis C, which confirms a consensus of elevated liver enzymes in HCV patients [33].

4. Conclusions

Liver enzymes are key indicators of human health and wellbeing. Although, they are ordered routinely, there are still some clinical and research uncertainties about their variation in key liver diseases. Therefore, we conducted a multi-disease evaluation for assessment of liver enzymes. Our results showed a significant change in the liver enzymes across different disease models. The level of liver enzymes varied across diseases and were highest in alcoholic hepatitis (ALT), autoimmune hepatitis and obstructive jaundice (ALP), while obstructive jaundice showed female predilection for AST. As liver diseases can pose a treatment challenge, therefore, a judicious and expeditious evaluation of liver enzymes must be performed for an excellent prognosis and clinical outcome.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Statement of informed consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. All procedures involving human participants were conducted in accordance with ethical standards.

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