DISCUSSION

Schistosomiasis, a debilitating disease endemic in 74 countries of the developing world, it affect 207 million people as reported in 2006[193], as recent articles documented infection of 391–597 million people, with 800 million, mostly children, at risk of the infection [194-196]. Additionally, schistosomiasis cause the annual loss of between 1.7 and 4.5 [193], but between 24 and 56 [194], and up to 70 [195,196] millions disability adjusted life years.

Egyptian health authorities and public media continuously advocate the near elimination of schistosomiasis from Egypt, statement that was not denied by the patients in rural populations because of the stigma of poverty and social status inferiority linked to this infection. Yet, several articles documented that Egypt has more than 10 million persons infected with schistosomes[194,197,198]. An article published in 2012 reports that Egypt is the country with the highest prevalence (7.2 out of 80.4 million patients, about 9%) of schistosomiasis [199].

The presence of both HCV and *Schistosoma* spp. is of significant concern as patients with coinfections have been shown to have higher HCV RNA titers, increased histological activity, and greater incidence of cirrhosis/hepatocellular carcinoma, and higher mortality rates than patients suffering from single infections[200].

The relationship between malnutrition and liver disease has been assuming greater significance due to the recognition that it is associated with adverse clinical outcomes. Malnutrition is present in 65-90% of patients with advanced liver disease and in almost 100% of candidates for liver transplantation [201,202]. Cirrhotic patients who are malnourished not only have a higher morbidity, but also an increased mortality rate.[203,204] The severity of malnutrition correlates directly with the progression of the liver disease.[205,206]

The present study aimed to evaluate the nutritional status of hepatitis C virus infected patients in association with schistosomal hepatic periportal fibrosis.

This study showed that the two studied groups (single infection and mixed infection) had malnutrion compared to the controls group. The degree of malnutrition was more severe in Group II that had mixed schistosomiasis and HCV infections.

The anthropometric measurements were more affected in Group II. The mean weight was 75 Kg in Group II, 79 Kg in Group I and 87 Kg in controls. The mean waist was 88.29 cm in Group II, 91.65 cm in Group I and 100.87 cm in controls. The mean waist-hip ratio was 0.82 in Group II, 0.87 in Group I and 0.90 in controls. The mean Fat percent in Group I was 17.56 %, in Group II was 14.95 % and 24.69 % in controls. The mean Body Mass Index in Group I was 26.81, in Group II was 25.94 and 29.21 in controls.

Waist–hip ratio or waist-to-hip ratio (WHR) is the ratio of the circumference of the waist to that of the hips. WHR is used as a measurement of obesity, which in turn is a possible indicator of other more serious health conditions. World Health Organization states that abdominal obesity is defined as a waist–hip ratio above 0.90 for males and above 0.85 for females.[207]

The body mass index (BMI), or Quetelet index, is a measure for human body shape based on an individual's mass and height. It is defined as the individual's body mass divided by the square of their height – with the value universally being given in units of kg/m^2.[208] The current value settings are as follows: a BMI of 18.5 to 25 may indicate optimal weight, a BMI lower than 18.5 suggest the person is underweight, a number above 25 may indicate the person is overweight, a number above 30 suggests the person is obese.[209]

Bioelectrical impedance analysis (BIA) is a commonly used method for estimating body composition, and in particular body fat. Since the advent of the first commercially available devices in the mid-1980s the method has become popular owing to its ease of use, portability of the equipment and its relatively low cost compared to some of the other methods of body composition analysis. It is familiar in the consumer market as a simple instrument for estimating body fat. BIA actually determines the electrical impedance, or opposition to the flow of an electric current through body tissues which can then be used to calculate an estimate of total body water (TBW).[210]

The chief reason for the malnutrition in these patients is poor oral intake, which may be due to a variety of causes. Vitamin A and or Zinc deficiency may give rise to an altered sense of taste. [217] The dietary restrictions that are frequently advised to these patients, such as restriction of salt, protein, and fats, can discourage adequate oral intake by rendering food a bland taste. Weakness, fatigue, and encephalopathy may also contribute to decreased oral intake. [218]

Malabsorption is another vital reason why patients with advanced hepatic disease become malnourished. A reduction in the bile-salt pool may lead to fat malabsorption,[219] or bacterial overgrowth may result from impaired small-bowel motility.[220] Portal hypertension has also been named as a cause of malabsorption and protein loss from the GI tract.[221,222] In addition, the administration of medications used in the treatment of hepatic encephalopathy may also contribute to malabsorption, anorexia, gastrointestinal congestion and portal hypertension.[223]

The functional integrity of the liver is essential for the utilization of nutrients. The liver influences the nutritional status by its production of bile acids and its role in the intermediate metabolism of proteins, carbohydrates, fats and vitamins.[225]

Both acute and chronic liver injuries frequently have nutritional consequences directly proportional to their severity which may progress to hepatic cirrhosis. [225]

Hepatic cirrhosis is characterized by chronic and irreversible alteration of the liver parenchyma due to modifications of both hepatic structure and of the functional capacity of the hepatocytes and of the portal circulation. [225] Together, these alterations result in a progressive loss of liver size and function, compromising to a varying extent the nutritional status and body homeostasis of patients affected by the disease. [225]

Hepatic cirrhosis is multifactorial and, according to its etiology, can be classified as metabolic, viral, alcoholic, drug-induced, autoimmune, biliary, and cryptogenic. [225] One of the methods used to assess the prognosis of hepatic disease is the Child-Pugh (CP) classification, which considers five factors that may affect prognosis and survival, i.e., ascites, hepatic encephalopathy, bilirubin and albumin levels, and prothrombin time.[226]

Unfortunately, this classification does not consider the nutritional status. Although albumin is considered to be a marker of nutritional status, in this case it may be altered due to changes inherent to the hepatic disease itself, malnutrition and due to decreased synthesis by the diseased liver. According to the score obtained, patients can be classified as Child-Pugh class A (mild), B (moderate) and C (severe). [226]

Alberino *et al* demonstrated that malnutrition is an independent predictor of survival and that the inclusion of arm muscle circumference (AMC) and tricipital skin fold (TSF) improves the prognostic precision of the CP classification. Thus, it is probable that nutritional status could be a useful addition to CP classification in the evaluation of the prognosis of cirrhotic patients.[227] The problem is that these anthropometric measures depend on the training of the anthropometrist and are not precise.

Although the CP classification has been the model most widely used to assess the prognosis of cirrhotic patients, its use is limited in individuals with closely similar laboratory markers and due to the subjective nature of measurements for the quantitation of ascites and encephalopathy. Thus, as an alternative for the assessment of prognosis, the Model End-Stage Liver Disease (MELD) has been used. [226] This model uses three laboratory indices: international normalized ratio (INR), bilirubin and serum creatinine and can discriminate in a more effective manner between patients who are likely to die and patients who will survive for at least three months.[228] Like the CP classification, the MELD does not incorporate measurements of nutritional status. The potential prognostic value of adding nutritional status to both the CP classification and the MELD is unknown.

Nutritional status is considered to be a predictor of morbidity and mortality in patients with advanced hepatic disease. Malnutrition also has important implications in liver transplantation and it has been demonstrated that patients with a worse nutritional status before the transplant have increased postoperative complications and higher mortality rates. [229]

In a study on 300 patients, Carvalho *et al* [230] showed that more than 55% of those with advanced hepatic disease had some degree of malnutrition, which was moderate to severe in 40%. In the same study, 95% of Child-Pugh class C patients were malnourished, as also were 74% of class B and 46% of class A patients.[230] The high prevalence of malnutrition even in patients in the early stages of the disease is a source of concern. Among the causes of malnutrition in these patients, particularly important are insufficient food intake, malabsorption and metabolic disorders. [229] Insufficient food intake may be caused by a series of factors. As is the case for other chronic diseases, anorexia makes a significant contribution to malnutrition, possibly being caused by physical symptoms of discomfort such as nauseas, congestion, fatigue and vomiting. Patients with ascites often have early satiety resulting from the mechanical effects of ascitic fluids that compress the stomach. [229]

In addition, the loss of appetite may be related to the increased regulation of inflammation and of appetite mediators. Besides the hormonal influences and physical discomfort, the lack of interest in food may result from food restrictions and changes in taste. [229]

Dietary limitations such as sodium restriction for the control of ascites, preoperative fast, and limitation of protein intake due to severe hepatic encephalopathy may reduce the

variety of foods and many patients do not accept the recommended foods. Although changes in taste may be commonly attributed to micronutrient deficiencies, several investigators have questioned whether they might be a consequence of cirrhosis itself. [229]

It is also important to consider the anorexia related to alcohol. According to the American Liver Foundation, 10% -20% of chronic alcohol users develop cirrhosis. A poor and irregular diet is common among patients with alcoholic cirrhosis. [229]

Malabsorption may be caused by pancreatic insufficiency and cholestasis and may be related to drugs that cause diarrhea (lactulose, antibiotics, diuretics, and cholestyramine).[229] Several mechanisms can lead to the malabsorption of nutrients, fats in particular, in cirrhotic patients. A complication that affects nutrient absorption is the portosystemic shunt. With the progression of cirrhosis, the nutrients bypass the liver through the portosystemic shunt without being processed metabolically. [229] In addition, many patients with cirrhosis due to alcohol abuse have chronic pancreatitis, which contributes to malabsorption. [229]

Another factor that leads to fat malabsorption in patients with cirrhosis is bile deficiency, which impairs the formation of micelles and the absorption of long-chain fatty acids through the usual lymphatic system. Portal absorption of these fatty acids may also occur in patients with cirrhosis. [229]

Among the metabolic disorders we may mention hypermetabolism during complications such as infections, hemorrhage, decompensation and ascites; increased protein catabolism due to inflammation and impaired hepatic synthesis; reduced glucose homeostasis due to hepatic insulin resistance caused by changes in gluconeogenesis, low glycogen stores and impaired glycogenolysis; increased lipolysis and lipid oxidation, and proinflammatory cytokines (TNFα, interleukins and leptin). [229]

Malnutrition may also be related to iatrogenic causes involved in investigative procedures, to fasting periods, protein restriction during periods of encephalopathy, and to large volumes of paracentesis. [229]

Energy expenditure is also known to contribute to the decline of nutritional status.[229] while most cirrhotic patients have resting energy expenditure (REE) similar to predicted values, 15% to 30% of them are hypermetabolic. Hypermetabolism may be defined as an REE of 120% compared to predicted values.[229]

The nutritional assessment of these patients is a challenge and should be performed with caution since changes inherent to the liver disease itself such as edemas, ascites and protein changes impair this task, preventing the use of the more traditional parameters for nutritional assessment. The 2006 guidelines of the European Society of Enteral and Parenteral Nutrition (ESPEN) recommend the use of subjective global assessment (SGA), anthropometric analysis and hand grip strength test (HGS) to identify patients with cirrhosis who are at risk for malnutrition. [229] SGA is a rapid tool for assessment used to collect information about food intake, changes in weight and gastrointestinal symptoms, including observations of loss of subcutaneous fat, loss of muscle mass, edema, and ascites. This tool is commonly used to assess patients with hepatic disease because it is simple and inespensive. [229]

Although the traditional anthropometric measurements such as weight, arm circumference and tricipital skin fold are considered to be adequate for the determination of the nutritional status of cirrhotic patients, this assessment should be careful. Albumin is a poor nutritional marker because it is typically reduced in patients with advanced hepatic disease and fluctuates during periods of inflammation.[229]

The HGS measures the strength of hand and forearm muscles. It is a simple and rapid tool for the assessment of nutritional status, although its use as a single evaluation has not been well established. [229] The muscle strength test was compared to SGA in cirrhotic patients and proved to be a superior predictor of clinical complications such as decompensated ascites, hepatic and bacterial encephalopathy, peritonitis and hepatorenal syndrome. Malnutrition starts within the cells with disequilibrium of the electrolytes, and muscle function can reflect this more rapidly.[229]

Thus, SGA, anthropometric measurements and the HGS are more commonly used in routine nutritional assessment. However, there is no gold standard method of easy application and low cost, without subjective data and not influenced by the professional who performs it. [229]

The analysis of bioelectrical impedance (BIA) is a sensitive, reproducible, safe and inexpensive method that can be used to determine nutritional status. This method is based on the property of the body of conducting an electric current, which has been known for hundreds of years. Tissues with a greater amount of water, due to the dissolution in electrolytes, are the major pathways of electric conduction, while body fat and bones are considered to be worse conductors. [231] A low alternating electrical current is conducted through a pair of electrodes while another pair, in which impedance is measured, measures the fall in tension. BIA measures parameters such as resistance (R) and capacitance (Xc), recording the fall in tension in the applied current. This change in tension is quantitated geometrically as the angular transformation of the proportion of capacitance to resistance, or phase angle (PA). The PA reflects the relative contribution of fluid (resistance) and cell membranes (capacitance) of the human body. [231]

Lean and fat body mass can be calculated. Lean mass is proportional to the amount of water, considering 53.2% water constant in lean mass. When lean mass is subtracted from weight, fat mass is obtained. Since cirrhotic patients usually have fluid retention and ascites, i.e., they do not have a normal distribution of body water, this calculation of lean mass and fat mass is not indicated.

However, the PA has been used as a prognostic marker in various clinical conditions in which the integrity of the cell membrane is compromised and changes in fluid balance are observed, such as the malnutrition of advanced neoplastic diseases. This measure has several advantages such as being independent of regression equations and the fact that it can be calculated even in situations in which it is not possible to estimate body composition. In a recent study, Fernandes *et al* found that the PA is the only parameter for nutritional assessment that is correlated with the severity of hepatic disease assessed by the CP classification and emphasized the importance of establishing a cut-off point as a parameter for the classification of malnutrition in the population of cirrhotic patients.[231]

Thus, the interest in comparing the PA to other methods used for the nutritional assessment of cirrhotic patients is clearly justified, in order to obtain data about its

performance as an indicator of the nutritional status of these patients. In addition, a precise, low-cost and reproducible nutritional parameter could be included in the Child-Pugh and MELD equations, contributing to a better prognosis for patients.

The present study discussed the clinical presentation of the studied groups. In Group I, 100 % of the patients had abdominal pain, 9.7 % had constipation, 48.8 % had hyperacidity, 22.6 % had regurgitation, and 6.6 % had piles.In Group II, 100 % of the patients had abdominal pain, 19.4 % had constipation, 29 % had hyperacidity, 19.4 % had regurgitation, and 3.2 % had bleeding per gum.

Schistosomal involvement of the liver is an excellent model of the study of immunologic liver injury, fibrosis and hemodynamic disturbances in the absence of parenchymal injury[232]. It may occur with all species of human schistosomiasis but is especially severe with S. mansoni and S. japonicum, both in acute and chronic phases of the disease.[233] HSS is a chronic liver disease characterized by granulomatous reaction, portal fibrosis, pre-sinusoidal portal hypertension, splenomegaly, hypersplenism, esophageal varices and haemorrhage.[234] The relative risk to develop hepatosplenomegaly in persons infected with *S. mansoni* have been reported in correlation with HLA-A1 and B5[235]. In advanced HSS, there is excess collagen deposition, mainly in the portal tract and Disse's space with obstruction of sinusoidal fenestration, resulting in fibrosis and capillarization of sinusoids.[236] According to whether the larger or small portal tract is mainly involved, Hashem[237] classified schistosomal hepatic fibrosis into coarse (first described by Symmers in 1947) and fine types. The term schistosomal cirrhosis is no longer used, as nodular regeneration and diffuse distortion of hepatic lobular architecture are not the features of hepatic schistosomiasis. The parenchyma between fibrotic areas is typically well preserved, correlating with the maintenance of nearly normal hepatic function, one of the clinical hallmarks of HSS.[239] Diagnostic procedures include demonstration of ova in stool or in rectal snip, ultrasonography of the liver which reveals characteristic periportal fibrosis and sometimes distention of portal and splenic veins exceeding 12 or 10 mm width respectively, upper GI endoscopy which demonstrates esophageal and/or fundal varices and finally liver biopsy which shows Symmer's or pipe-stem fibrosis.[239]

Several authors reported a higher frequency of chronic hepatitis B or C in patients with hepatosplenic schistosomiasis than in normal control subjects.[240-243] A statistical correlation between previous parenteral therapy for schistosomiasis and the presence of HBsAg and HCV-Ab were reported in many studies.[243-246] It was also proposed that these patients had an impaired immune response that enhanced their susceptibility to becoming chronic carriers.[247] Concomitant infection with both schistosomiasis and hepatitis B or C causes more severe liver disease than infection with schistosomiasis alone.[248] The prognosis for this group of patients was worse than that observed by either schistosomiasis or chronic hepatitis B or C as isolated problems.[249] Depressed immunity may also account for chronic salmonellosis infection that often complicates advanced hepatosplenic schistosomiasis. There are prolonged fever and positive blood culture lasting for months and raised level of transaminases as a manifestation of non-specific hepatitis. It can only be cured by both antibacterial and antischistosomal agents.[250]

The course of schistosomiasis on the liver involves both direct effect as well as indirect effect of both intravenous therapy and molluscicides used for combating the snail

intermediate hosts. The direct effect is represented by ova deposition in the portal tributaries with granuloma formation, which is replaced overtime by periportal fibrosis and hepatosplenomegaly. Subsequently, portal hypertension may result in the development of esophageal varices and variceal bleeding. Ascites and hepatic coma are the end-stage findings. The indirect effect is represented by both transmission of hepatitis B and hepatitis C through improperly sterilized glass syringes [(251)] used at that time. In the meantime schistosomiasis induced immune suppression could result in increased persistence of viraemia following acute infection of both hepatitis B and C.[(252)] This could partially explain the increased prevalence of HCV in Egypt. El-Zayadi *et al*. [(253)] pointed out that the hepatotoxic effect of Potassium antimony tartarate (tartar emetic) was a heavy metal like arsenic used as therapy in the development of portal fibrosis and angiosarcoma. Furthermore, the spray of cupper sulphate in canals to combat the snail intermediate hosts has been proved to have a hepatotoxic effect which was incriminated in the pathogenesis of angiosarcoma, hepatocellular carcinoma and cirrhosis.[(254)] Recently, this gloomy picture has been dramatically changed with adoption of effective control measures and the use of oral therapy for schistosomiasis. In the meantime, the use of disposable syringes has reduced the risk of transmission of HBV and HCV.[(254)]

The present study showed differences in the complete blood picture between the studied groups. In Group I, the mean RBCs count was 4.70. In Group II, the mean RBCs count was 4.13. In Group I, the mean hemoglobin concentration was 12.23 gm/dl. In Group II, the mean hemoglobin concentration was 11.01 gm/dl. In Group I, the mean WBCs count was 6.52. In Group II, the mean WBCs count was 6.23. In Group I, the mean platelets count was 195.13. In Group II, the mean platelets count was 127.58.

Chronic liver diseases frequently are associated with hematological abnormalities. Anemia of diverse etiology occurs in about 75% of patients with chronic liver disease.[(255)] A major cause of anemia associated with chronic liver disease is hemorrhage, especially into the gastrointestinal tract. Patients with severe hepatocellular disease develop defects of blood coagulation as a consequence of endothelial dysfunction, thrombocytopenia, deficiencies of coagulation factors and various associated disorders.[(256)] In severe hepatocellular disease, decreased synthesis of liver-produced plasma proteins leads to reduced serum levels of several blood clotting factors. Hemorrhage may occur as a complication of chronic liver disease because of a lack of one or more liver-produced blood clotting factors, thrombocytopenia, and/or defective platelet function. Hemorrhage in such patients may also occur from esophageal or gastric varices secondary to portal hypertension. The biosynthetic pathways of blood coagulation factors are within the hepatocyte and are dependent on vitamin K.[(257)]

Low serum levels of these factors are associated with prolongation of the prothrombin time (PT). When attributable to hepatocellular disease, they are not improved by administration of vitamin K; correction of the associated impaired blood coagulation necessitates infusion of preparations of the deficient factors. Splenomegaly, which is usually caused by portal hypertension in patients with chronic liver disease, may lead to secondary hemolysis, an increase in plasma volume, macrocytosis and megaloblastic anemia. Alcohol, a common etiologic factor of chronic liver disease, is toxic to the bone marrow. Alcoholics often develop secondary malnutrition, a manifestation of which may be anemia caused by folic acid deficiency. In some patients, bone marrow failure and aplastic anemia develop after an episode of hepatitis. Finally, anemia is a recognized

complication of treatment of chronic hepatitis C with a combination of interferon and ribavirin: anemia in this context is predominantly caused by ribavirin-induced hemolysis.[258] The frequent association of anemia with chronic liver disease and/or hepatocellular failure provides a rationale for examining the role of the liver in the formation and destruction of erythrocytes. Indeed, the liver itself may be implicated in a variety of different mechanisms that contribute to the development of anemia in patients with chronic liver disease.[258]

Hypersplenism secondary to portal hypertension is another mechanism of anemia in patients with chronic liver disease. Hypersplenism is associated with splenomegaly. In addition to chronic liver disease, thrombosis of the splenic vein may also be a cause of an increase in pressure within the portal venous system, which can lead to secondary hypersplenism. The main characteristics of hypersplenism are those attributable to pancytopenia. Hemolytic anemia occurs because of intrasplenic destruction of erythrocytes. Destruction of megakaryocytes and leukocyte precursors results in thrombocytopenia and leukopenia.[259]

Symptoms and signs of hypersplenism are influenced by the primary underlying disease; they include abdominal pain and/or discomfort, and, in advanced cases, gastrointestinal hemorrhage secondary to portal hypertension. There may be hyperplasia of the progenitor cells in the bone marrow. It is important to determine the cause of hypersplenism. The main therapeutic approach for this syndrome is management directed at the underlying primary disease, usually chronic liver disease. When chronic liver disease is advanced, additional therapeutic options may need to be adopted. After assessing the severity of impaired hepatocellular function in a patient with advanced chronic liver disease, splenectomy may be considered if the splenic vein is thrombosed. An alternative approach is partial or total embolization of the splenic artery, which, in some recent studies, has been associated with good results, in particular, lower morbidity and mor tality rates than those associated with surgery. Partial embolization preserves the immunological function of the spleen and is the preferred option for patients with cirrhosis.[260]

The liver plays a central role in blood coagulation. Acute and chronic hepatocellular diseases are usually associated with defective blood coagulation due to a variety of different causes. These include: decreased hepatic synthesis of coagulation factors; the presence of inhibitors of these factors; decreased clearance of activated coagulation factors; thrombocytopenia; impaired platelet function; hyperfibrinolysis; and disseminated intravascular coagulation.[261,262] Coagulation defects complicating liver disease predispose to an increased bleeding tendency, which increases both morbidity and mortality .[261-263]

Defective blood coagulation associated with hepatocellular disease may be monitored using global screening tests, such as the PT and the activated partial thromboplastin time. In mild hepatocellular disease, PT usually is within the normal range or only modestly prolonged. In more advanced hepatocellular disease, prolongation of PT tends to reflect the severity of hepatocellular failure. Vitamin K routinely is administered parenterally (usually only once) to patients with liver disease and a prolonged PT, to exclude vitamin K deficiency as a cause of the prolonged PT.[261]

Thrombocytopenia (platelet count < 150 000/L) is common in patients with chronic liver disease; it has been reported in as many as 76% of patients with cirrhosis.[262] The pathogenesis of the thrombocytopenia is complex; it includes splenic pooling, and

increased destruction and impaired production of platelets . Impaired production of platelets is caused, at least in part, by low levels of thrombopoietin. Prolonged bleeding time, and impaired aggregation, reduced adhesiveness and abnormal ultrastructure of platelets reflect abnormal platelet function; these abnormalities have been attributed to an intrinsic platelet defect. Specific treatments to attempt to reverse the effects of this defect are not usually given, but platelet transfusions or platelet stimulating agents have been administered in some cases. An important coagulation defect associated with chronic liver disease is low levels of coagulation factors. In recent years, the hemostatic agent recombinant factor A has become available as a potentially new therapeutic agent for use in the management of coagulopathy in patients with cirrhosis. This agent may enhance initial control of acute variceal bleeding. However, such therapy is associated with significant side effects, such as vascular injury and thrombosis. [264]

Hyperfibrinolysis is another cause of impaired hemostasis in patients with liver disease. In a nonrandomized trial, antifibrinolytic amino acids were administered to patients with acute or chronic liver disease, who had upper gastrointestinal bleeding and acquired defects of blood coagulation. However, administration of such amino acids does not have an established place in therapy. Thrombotic events, although rare in patients with cirrhosis, may occur. They tend to involve particularly the portal and/or mesenteric veins. A rational approach to managing disorders of blood coagulation in patients with liver disease is important because of the high risk of associated secondary hemorrhage. [265]

Aplastic anemia associated with liver disease is characterized by development of pancytopenia and hypocellular bone marrow in relation to the occurrence of hepatitis.[266] The main feature of this syndrome is injury to or loss of pluripotent hematopoietic stem cells, in the absence of infiltrative disease of the bone marrow.[266-269] Hepatitis-associated aplastic anemia (HAA) has been defined as a variant of aplastic anemia, which occurs concurrently with or within 6 month of an increase in the serum level of alanine aminotransferase to at least five times the upper limit of the reference range. Severe marrow aplasia may be induced by hepatitis viruses, such as hepatitis B virus and hepatitis C virus (HCV), and also by other viruses, such as human immunodeficiency virus, Epstein-Barr virus, transfusion-transmitted virus and echovirus.[266,270] Parvovirus B19 commonly infects pro-erythroblasts and may induce transient red-cell aplasia, particularly in patients with chronic hemolytic anemia. It has been postulated that viruses and/or antigens, through the mediation of γ interferon or the cytokine cascade, induce lymphocyte activation and ultimately apoptotic death of hematopoietic cells in the bone marrow.[267]

Clinical presentation includes symptoms and signs related to pancytopenia, such as pallor, fatigue, hemorrhagic manifestations, progressive anemia, and bacterial infections. The diagnosis of HAA is suggested by a complete blood count, which reveals pancytopenia (including anemia) together with absolute reticulocytopenia.[266] A bone marrow biopsy typically reveals hypocellularity that affects red and white cell precursors and megakaryocytes; residual hematopoietic cells appear morphologically normal.[269] The two major options for treating severe HAA are hematopoietic cell transplantation and immunosuppressive therapy. According to recent reviews, response rates to these approaches are 75%-88% and 75%-80%, respectively. Blood and platelet infusions are often necessary before instituting specific treatment; before administration blood products should be irradiated to avoid sensitization. [266,268]

The present study showed that there were differences in the liver enzymes. In Group I, the mean ALT level was 38.19. In Group II, the mean ALT level was 44.48. In Group I, the mean AST level was 38.52. In Group II, the mean AST level was 45.71.

Fahim *et al*.(2000) found that the changes in the serum levels of liver enzyme activities in patients suffered from chronic schistosomiasis without or with HCV. A very highly significant increase of serum ALT activity was recorded in all studied groups except for schistosomal patients without organomegaly. Similarly, serum AST activity was significantly elevated in the previous groups. A statistically non significant change was recorded in AST/ALT ratio in all studied groups. (270)

Transaminases are sensitive indicators of liver cell injury and most helpful in recognizing acute hepatocellular diseases.They are also considered among the first laboratory abnormalities detected in the early phase of viral hepatitis.(271) Results obtained from this study demonstrate that combination of chronic schistosomiasis and viral hepatitis C manifested the highest elevation in serum levels of ALT and AST activities. It is noteworthy that the sharp rise of serum ALT and AST activities is more pronounced in the combined patients without liver cirrhosis and amounted to about 8 and 6 fold, respectively. A lesser increase of about 4 and 5 fold was recorded in the combined patients with decompensated liver cirrhosis. The mechanism of hepatocyte and bile duct injury that occurs with HCV infection is unknown, but it may be due to a combination of two mechanisms, direct cytopathic effect of HCV and immune-mediated cell injury triggered by HCV.(272) Serum AST/ALT ratio is important to differentiate acute and chronic viral hepatitis. It is reported that AST/ALT ratio is a dependable marker of fibrosis stage and cirrhosis and that its value is significantly decreased below 1 in acute HCV, while in chronic viral hepatitis although AST/ALT ratio is slightly decreased, yet it is still more than 1.(273) Data illustrate that serum AST/ALT ratio showed no significant decrease compared to normal controls, yet the highest value is recorded in the combined group with liver cirrhosis. Michielsen *et al*. attributed the elevation in AST/ALT ratio in case of cirrhosis to the higher rise of serum AST activity probably because this cytosolic and mainly mitochondrial enzyme is present in higher quantities in the liver, compared to the cytosolic ALT and thus more is released in tissue damage. (274)

AST, (GOT) and ALT (GPT) have been suggested for the two enzymes of greatest clinical significance in viral hepatitis and other forms of liver disease associated with hepatic necrosis serum AST (GOT) and ALT GPT) levels which are elevated even before the clinical signs and symptoms of disease (such as jaundice(appear. Levels for both enzymes may reach values as high as the upper limits of the reference interval) .274)

Albumin, produced only by the liver, is the major protein that circulates in the blood. Albumin consists of 585 amino acids, has a molecular weight of approximately 69 kDa and is the most abundant plasma protein, although 60% of the total albumin pool is in the interstitial space. (275) Albumin is essential for maintaining the oncotic pressure in the vascular system. A decrease in oncotic pressure due to a low albumin level allows fluid to leak from the interstitial spaces into the peritoneal cavity, producing ascites. Albumin is also very important in the transportation of variousmolecules, including bilirubin, free fatty acids, drugs, and hormones. Serum albumin is an abundant multifunctional non-glycosylated, negatively charged plasma protein, with ascribed ligand-binding and transport properties, antioxidant functions, and enzymatic activities. (276)

The present study showed that there were differences in albumin level. In Group I, the mean albumin level level was 3.70 mg/dl. In Group II, the mean level was 3.12 mg/dl.

A low serum albumin concentration indicates poor liver function. Decreased serum albumin levels are not seen in acute liver failure because it takes several weeks of impaired albumin production until the serum albumin level drops. The most common reason for a low albumin is chronic liver failure caused by cirrhosis. The serum albumin concentration is usually normal in chronic liver disease, until cirrhosis and significant liver damage develops. In advanced liver disease, the serum albumin level may be less than 3.5 g/dl. The albumin level is clinically important as apredictive factor for patients with liver cirrhosis, because decreased serum albumin levels cause ascites and edema. Recent studies have demonstrated the efficacy of branched-chain amino acid (BCAA) supplementation in improving hypoalbuminemia in cirrhotic patients.[277] Kotho *et al*. investigated the correlation between albumin levels and the fat-free mass in cirrhotic patients. They showed that exercise and protein rich nutrition at the early stage of liver cirrhosis may be advisable for maintaining or increasing muscular volume.[278]

This study showed that In Group I, the mean cholesterol concentration was 143.94 mg/dl. In Group II, the mean Cholesterol concentration was 143.42 mg/dl. In Group I, the mean Triglycerides concentration was 118.13 mg/dl. In Group II, the mean Triglycerides concentration was 118.42 mg/dl.

Clinical evidence indicates that HCV infection is not only intimately linked to the metabolism of lipids within the hepatocytes that HCV infects, but dysregulates circulating lipoprotein metabolism as well. The liver is the central organ of lipid homeostasis for the entire body, through production and uptake of lipoproteins. Triglycerides (TG) are packaged in lipoproteins surrounded by a phospholipid, cholesterol, and amphipathic protein monolayer to deliver lipids produced or absorbed from the liver and intestine respectively to other organs. [279]

Aside from the physical association of HCV components with lipoproteins, intracellular lipids play key roles throughout the HCV life cycle. HCV replication requires numerous factors involved in lipid metabolism and HCV assembly and production depends on elements of VLDL assembly. Chronic HCV infection is associated with deregulated lipid homeostasis favoring triglyceride accumulation in the liver.[280] HCV infection may contribute to this accumulation through transcriptional activation of lipogenic genes favoring lipid synthesis in HCV patients.[281]

The present study showed differences in Leptin levels, it was significantly higher in Group II. In Group I, the mean Leptin level was 5.54 ng/dl. In Group II, the mean Leptin level was 6.18 ng/dl.

Hepatic steatosis is a histopathological feature observed in more than 50% of patients with chronic hepatitis C (CHC) [286], but occurs less frequently in patients with chronic hepatitis B (27%-51%) and autoimmune hepatitis (16%-19%).[287] Steatosis in CHC patients has been attributed to a combination of mechanisms involved in the pathogenesis of non-alcoholic fatty liver disease, as well as to the direct effect of hepatitis C virus (HCV) on hepatic lipid metabolism leading to triglyceride accumulation.[288] In contrast, steatosis in patients chronically infected with hepatitis B virus (HBV) is associated with host metabolic factors.[290]

Leptin is an adipokine that contributes to the pathogenesis of liver steatosis. In patients with CHC, higher serum leptin concentrations have been associated with the presence of steatosis. Although no clear correlation has been observed between leptin concentrations and the extent of steatosis[291], a recent study reported that high serum leptin concentrations correlated with more severe steatosis, lower viremia, and a lower antiviral response, mainly in patients infected with HCV genotype-1, which constituted 71% of the study population.[292]

Malnutrition is a common feature of cirrhotic patients.A negative energy balance, and thus catabolism caused by energy expenditure is considered to be of pathophysiological relevance in cirrhosis.[282] Several studies have shown that circulating leptin levels are modestly elevated in patients with alcoholic cirrhosis, suggesting that leptin might be involved in the malnutrition of cirrhosis.[283] While some studies have been supported these findings, others have reported low serum leptin levels in post-hepatitis cirrhotic patients.[284] In addition, nutritional status of cirrhotic cases represents a wide range in normal to severe malnutrition, connected with severity of the disease. It appears that relationship of serum leptin levels and nutritional status in post-hepatitis cirrhosis has not been fully clarified yet. [285]

Leptin is a link between HCV infection and steatosis.[293] Although a high incidence of hyperleptinemia has been observed in HCV infected patients with liver steatosis[294], the underlying mechanism promoting this effect remains undefined. Leptin may increase insulin resistance and fatty acid concentrations in the liver, leading to enhanced lipid peroxidation and promoting steatosis.[294]

HCV infected patients with liver steatosis, serum leptin levels tend to increase as the grade of steatosis worsens. This finding is significant, especially in genotype-1 patients, suggesting that leptin increases during infection as a part of the host immune response, and may contribute to the development of steatosis. [295]

The associations among HCV, liver steatosis, and fibrosis have driven research (2004) into the evaluation of the roles of leptin and adiponectin. Increased serum leptin levels were higher in 30 CHC patients than in 30 controls. [296] In two studies, leptin levels were found independently associated with fibrosis severity, while a possible relation with steatosis was not evaluated or not found .[297] In 131 CHC patients, leptin levels were found to be associated with steatosis in genotype 1 but not in genotype 3 patients, and this association remained unchanged after exclusion of 37 heavy drinkers. A weak association between leptin levels and fibrosis severity was also reported. In 48 CHC patients with steatosis but without diabetes, obesity, hyperlipidemia, and alcohol abuse, leptin levels did not correlate with fibrosis or steatosis severity. [298]

Muzzi *et al.* in a multicenter study including 221 nondiabetic CHC patients stated that there was no correlation between leptin levels and histological features regardless of genotype, while Insulin resistance was associated with fibrosis in the 152 non genotype-3 patients.[299] In another study, leptin levels were found to be associated with steatosis in 74 CHC patients only in the univariate analysis, while no correlation was observed between leptin levels and necroinflammation or fibrosis.[300] Two additional studies failed to show any association of leptin in CHC, although they had significant findings for adiponectin . Finally, in a Spanish study, IR, fibrosis severity and genotype, but not leptin levels, were considered as the only predictors of sustained response to therapy.[301]

Wang *et al.* stated that serum leptin levels are increased in CHC patients, the data on their associations with histological lesions are rather conflicting. This may be due to the heterogeneity in the study populations. Leptin, however, is suggested to have no association with fibrosis or steatosis in cases without metabolic risk factors for hepatic steatosis.[302] Given the more frequent development of hepatic steatosis due to metabolic factors in genotype 1 infection, there may be an association between leptin levels and fibrosis and/or steatosis in genotype 1 but not in genotype 3 CHC patients. It should be noted that no study suggesting an independent association between leptin levels and fibrosis severity evaluated Insulin resistance Wang, which therefore might have been a hidden confounding factor. [303]