Study of Serum Magnesium in Liver Disease - A Cross-Sectional Observational Study Conducted in Bagalkot District, Karnataka

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ABSTRACT

BACKGROUND

Liver disease is considered as one of the major global burdens of disease in annual global burden of disease (GBD) analysis. In India, liver disease is the tenth most common cause of death. Trace element concentrations in liver diseases play a vital role in morbidity and mortality, they are markers of oxidative stress levels in the liver. Magnesium is the second most abundant intracellular cation and is a cofactor for many enzymatic reactions involving energy metabolism. Magnesium supplementation can improve liver function in liver diseases. This study comprehensively reviews the changes in magnesium concentrations associated with liver diseases.

METHODS

A cross-sectional observational study of 55 patients with acute and chronic liver diseases were included and the laboratory parameters like total bilirubin, serum magnesium etc. were collected from the patient, admitted in S. Nijalingappa Medical College and HSK Hospital, Bagalkot district Karnataka.

RESULTS

Total of 55 patients with liver diseases were included in our study, out of which majority of them were chronic liver disease patients with 61.8 %. Mean total bilirubin of the patients was more than 6 times the upper limit of normal (normal 0.2 - 1.0 mg %) which was 6.4 mg %, mean serum magnesium was lower than the normal, which was 1.73 mg/dl (normal 1.9 -2.9 mg/dl). Further we observed the possibility of link between the total bilirubin levels and the serum magnesium levels in all the patients with liver diseases, and it was noted that there is no correlation between the total bilirubin levels and serum magnesium levels, a non-significant relationship.

CONCLUSIONS

In our study conducted, patients with liver diseases presented with ascites, lower limb oedema, icterus, and some with hepatic encephalopathy. Majority of them are chronic liver disease, almost all of them had lower serum magnesium levels. The correlation between the level of serum magnesium and the total bilirubin levels of the patients in our study is observed and it showed negative correlation between level of total bilirubin and magnesium, a non-significant relationship.

KEYWORDS

Serum Magnesium, Liver Disease

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BACKGROUND

Liver is one of the source of substantial burden and cost in the United States.[1] Liver disease is considered as one of the major global burden of disease in annual global burden of disease analysis.[2] The key to understand the burden of liver disease is the incidence and prevalence of cirrhosis and primary liver cancer. It is stated that about 90 % of people in Europe infected by viral hepatitis are unaware of their status.[3]

Non-alcoholic fatty liver disease (NAFLD) is more common in US population.[4] Magnesium is the second most abundant intracellular cation and is cofactor for many enzymatic reactions involving energy metabolism, approximately half the total magnesium in the body is present intracellularly in soft tissue, and the other half is present in bone.[5]

The concentrations of trace elements among patients at various stages of liver cirrhosis, and also found a significant correlation between trace element metabolism and disease presence and progression. There is also a correlation between serum trace element concentrations and metalloprotein concentrations in the body, imbalances in which play a role in liver disease. Excess or deficiency can be rectified for improvement of liver disease. Because trace element concentrations are markers of oxidative stress levels in the liver, analysis of the concentrations can also be used for diagnosis of liver disease as well as indicating the effectiveness of antioxidant therapy.[6]

Most of the trace elements that have immunomodulatory and antimicrobial activities generally serve as enzyme-cofactors, antioxidants, and/or anti-inflammatory agents.[7] Impairments of the liver function result in disturbances of the metabolism of trace elements, leading to the initiation of oxidative stress and the subsequent inflammatory and/or fibrotic changes in the liver.

The impairment of homeostasis of trace elements leads to various inflammatory changes and/or metabolic abnormalities such as those observed in inflammatory bowel disease, diabetes mellitus, dyslipidaemia, and sarcopenia as well as chronic liver injuries.[7] Magnesium is a vital cation that takes part in many cellular processes. Magnesium balance can be disturbed in multiple conditions, and differences in magnesium concentration can be responsible for numerous physiological and pathological processes.

Magnesium is associated with more than 300 enzymatic reactions involving energy ATP/ADP metabolism, nucleic acid and protein metabolism. It is also involved in immune cell adherence, immunoglobulin synthesis, antibody-dependent cytolysis, T-helper B-cell adherence and additional responses.

Out of total body magnesium, only 0.3 % exists in serum. Magnesium deficiency is commonly associated with liver diseases, and may result from low nutrient uptake, greater urinary secretion, low serum albumin concentration, or hormone inactivation. Chronic terminal cirrhotics are magnesium depleted which should be taken into account in case of liver transplantation and also in other interventions.[8] In turn, low magnesium content in serum and liver tissue can lead to the progression of these diseases, due to disruption in mitochondrial function, defective protein kinase C (PKC) translocation, inflammatory responses, oxidative stress, or metabolic disorders.

Mechanisms which might cause depletion of body magnesium in the cirrhotic and alcoholic include poor dietary intake of magnesium, lack of renal conservation of magnesium, accelerated magnesium loss in the urine due to increase in aldosterone levels, the effect of alcohol on urine magnesium levels, and poor gastrointestinal absorption of dietary magnesium or increased loss of magnesium in feces.[9] Higher intakes of magnesium will be associated with reduced risk of mortality due to liver disease regardless of alcohol use or hepatic steatosis at baseline.[10]

It is even demonstrated that profound effect of Mg depletion on bone characterized by impaired bone growth, decreased osteoblast number, increased osteoclast number in young animals, and loss of trabecular bone with stimulation of cytokine activity in bone.[11] It was observed that the cellular level of ATP is markedly reduced after acute ethanol administration would suggest that Mg2+ extrusion results from a decreased buffering capacity of cytosolic Mg-ATP complex.[12]

Patients with liver cirrhosis usually have low body magnesium levels. Since our understanding of the mechanisms involved in magnesium homeostasis has improved, it has been shown that both serum and cellular magnesium levels are significantly lower in cirrhosis patients.[13]

According to a recent 2021 study published in the journal of hepatology,[14] it was found that both patients and mice that had non-alcoholic steatohepatitis also had high amounts of cyclin M4 (CNNM4) protein. This protein has a job of transporting magnesium out of the liver. It is the responsible party behind the imbalance of magnesium levels that can lead to liver disease development. Furthermore, magnesium supplementation can improve liver function in certain liver diseases. This study comprehensively reviews the changes in magnesium concentrations associated with liver diseases.

Aims

To study the levels of serum magnesium in acute and chronic liver diseases and to see any correlation between serum magnesium and serum bilirubin in acute and chronic liver disease.

METHODS

This is a cross-sectional observational study. The study was conducted after taking ethical clearance from the Institutional Ethics Committee of SNMC and HSK Hospital, Bagalkot, Karnataka, in the Department of General Medicine from December 2020 to July 2021.

Study Group
55 patients of liver disease admitted in wards and emergencies under the Department of General Medicine, after fulfilling all inclusion and exclusion criteria were included.

Sample Size Calculation
To achieve the objective of this study, input for statistical sample size calculation was taken from the study by Prakash Gurudevarahalli Made Gowda et al. (2015). Minimum required sample size with 'pedal oedema' taking as factor and p value is 72 % for 12 % error and for 95 % confidence level, by using "Open Epi version-2" software we got sample size 54, marginally we have taken the sample size of 55.

By using formula

$n = [DEFF * Np(1-p)]/ [d2/Z2\ 1-\alpha/2 * (N-1) + p * (1-p)$

Inclusion Criteria
Diagnosed cases of acute and chronic liver diseases.

Exclusion Criteria
1. Cases of hepatocellular Carcinoma,
2. Current treatment with magnesium supplements
3. Patients not willing for participation in the study.

Method of Data Collection
1. We collected data from 55 patients with confirmed cases of liver diseases who were admitted in S. Nijalingappa Medical College and HSK hospital from December 2020 to July 2021.
2. Basic investigation including complete blood count (CBC), renal function test (RFT), liver function test (LFT), serological test, and estimation of serum magnesium levels were carried out in all the patients included in the study.

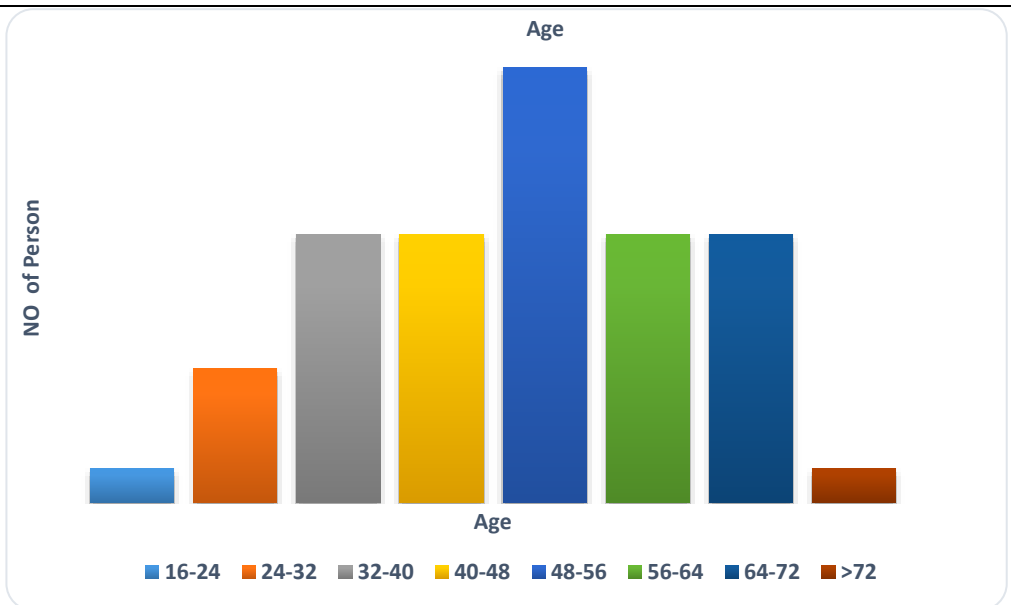
Statistical Analysis
Data were entered in Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) software version .19, percentages and proportions were used for qualitative data and mean and standard deviation for quantitative data. Chi-square test for proportions and student's t test was used for quantitative data. $P < 0.05$ is considered as statistically significant.

RESULTS

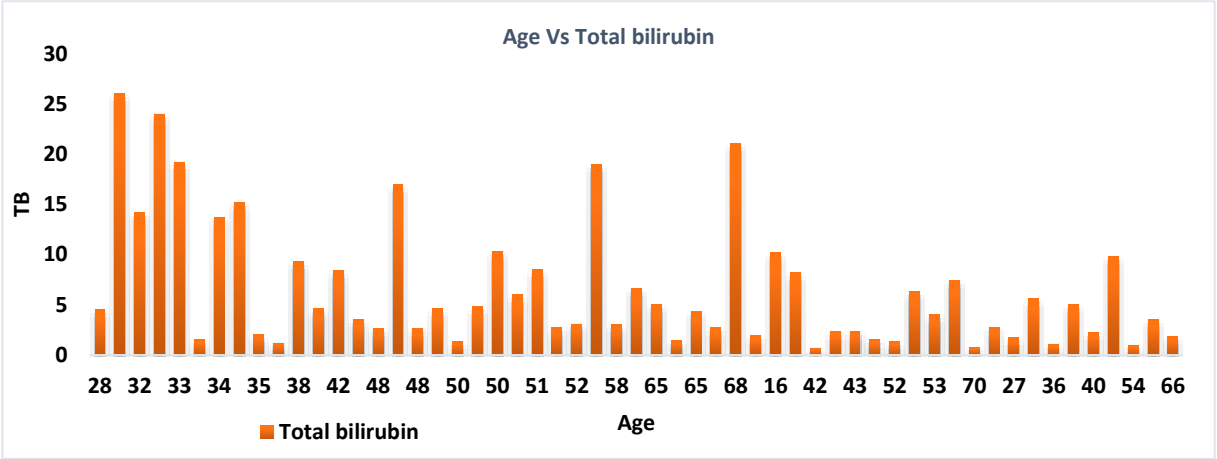
All of the enrolled 55 patients were diagnosed with liver disease. The age of the study population varied from 16 years to 76 years of age with mean age of 46.9 (Graph-1). Graph-2 and Graph-3 shows the distribution of total bilirubin and serum magnesium in different age group. The normal value of total bilirubin ranges between 0.2 to 1.0 mg %, the values of total bilirubin in our study population ranged from 0.7 to 26 mg %, with a mean of 6.457 (Graph-4).

The normal value of serum magnesium ranges between 1.9 to 2.9 mg %, the values of serum magnesium in our study population ranged from 0.9 to 2.7 mg %, with a mean of 1.73 mg % (Graph-5), showing the low level of serum magnesium in most of the liver disease populations in our study.

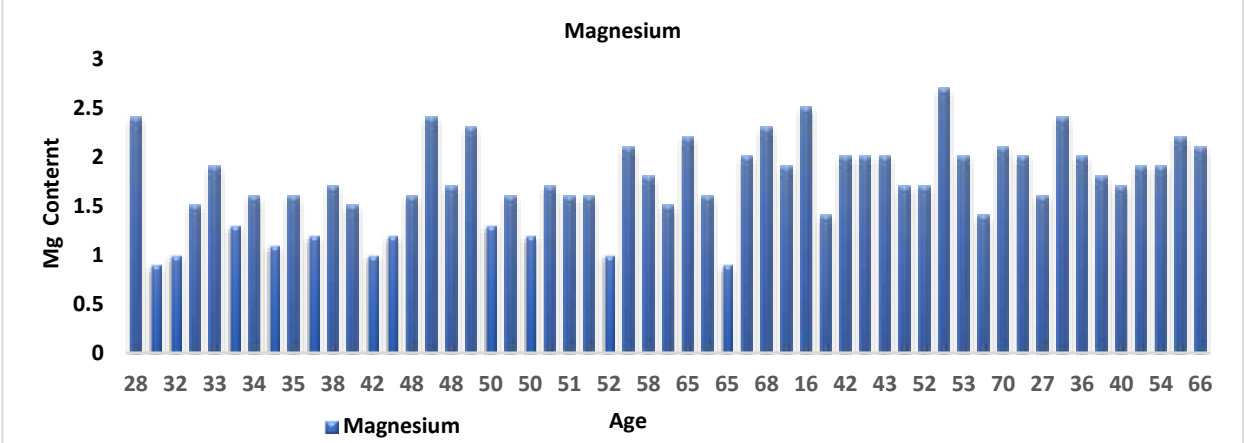
Further, we observed the possibility of link between the total bilirubin levels and the serum magnesium levels in all the patients with liver diseases, and it was noted that there is no correlation between the total bilirubin levels and serum magnesium levels, a non-significant (Table-1).



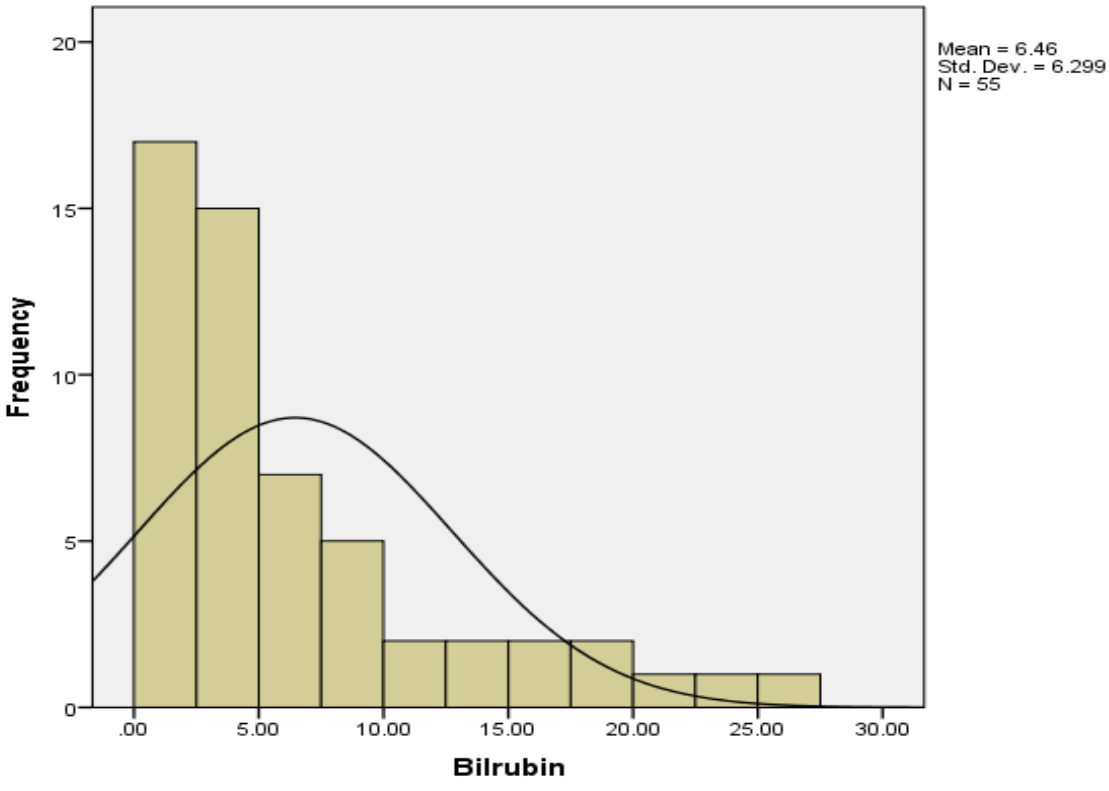
Graph 1. Age Distribution of Study Population



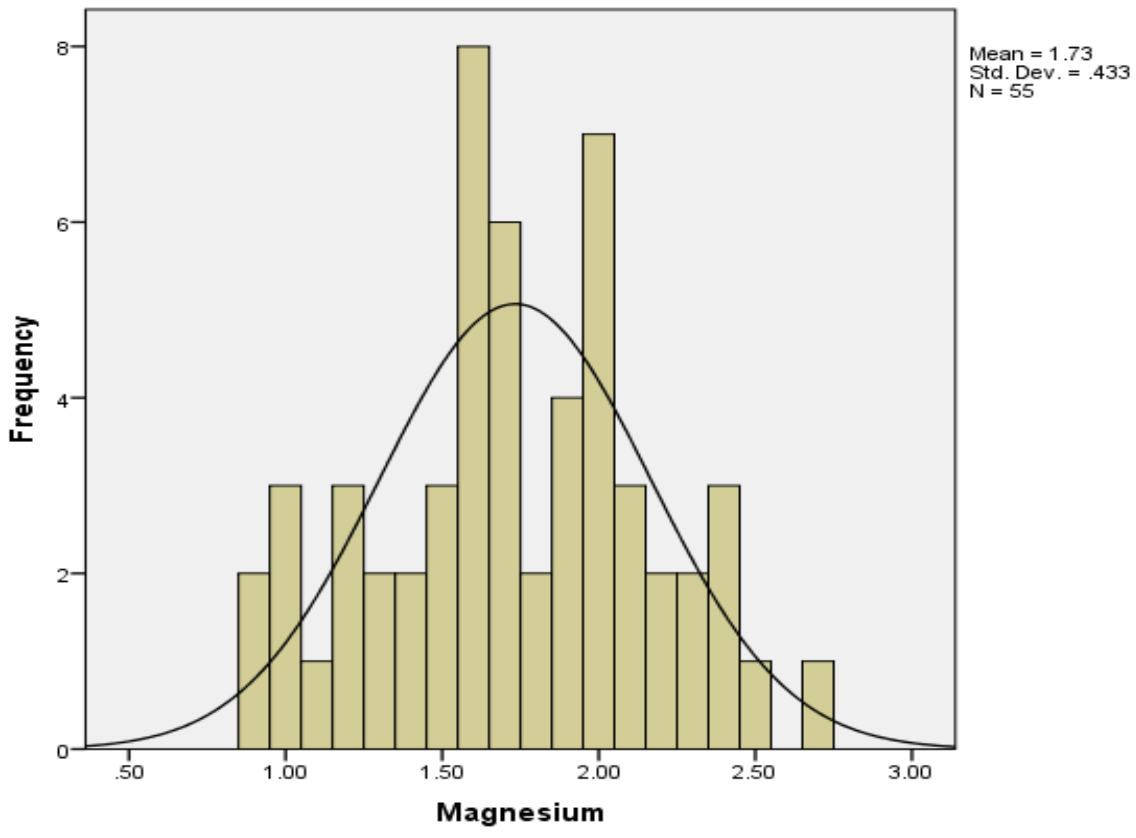
Graph 2. Comparison of Age of the Patient with Total Billirubin



Graph 3. Comparison of Age of the Patient with Serum Magnesium



Graph 4. Bilirubin Levels Observed in the Study Group



Graph 5. Serum Magnesium Levels Observed in the Study Population

Correlations			
		Magnesium	**Billirubin**
Magnesium	Pearson's correlation	1	-.091
	Sig. (1-tailed)		.255
	N	55	55
Bilirubin	Pearson's correlation	-.091	1
	Sig. (1-tailed)	.255	
	N	55	55

Table 1. Correlation between the level of serum magnesium and total bilirubin in liver disease patients

DISCUSSION

In this study, we considered magnesium as one of the vital element responsible for morbidity and mortality in its deficiency, in liver diseases patients. It was observed in our study, that there was magnesium deficiency in almost all of the liver disease patients. Magnesium is directly linked to liver function status. Liver diseases will have a remarkable effect on the body magnesium content, and magnesium levels in turn determine these disease processes. Serum zinc, magnesium, and selenium levels were significantly decreased with advancement of liver disease as compared to early stage of liver cirrhosis and showed a significant negative correlation with Child-Pugh score. Trace element abnormalities may reflect the condition of liver dysfunction. Liver dysfunction may alter the metabolism of trace elements. Some study showed that micronutrients status in liver cirrhosis correlates well with severity of liver cirrhosis. Micronutrients supplementation in liver cirrhotic patients may prevent progression of disease and development of complications.[15] In acute and chronic liver diseases, patients show magnesium deficiency that results from reduced dietary intake, increased urinary excretion, lower plasma albumin concentrations, and hormone inactivation. Conversely, magnesium deficiency aggravates acute and chronic liver diseases and can cause liver carcinoma progression, due to mitochondrial function, defective PKC translocation, inflammatory responses, oxidative stress, and metabolic disorders. Alcohol consumption is associated with a reduction in liver Mg^{2+} content.[16] Acute alcohol administration affects the Na^{+}/Mg^{2+} exchanger as follows. It affects G protein signalling, leading to greater cAMP generation within hepatocytes, which activates the PKC pathway and disrupts PKCε translocation to the cell membrane,[17-19] resulting in greater magnesium extrusion via the Na^{+}/Mg^{2+} exchanger. Biochemical analysis also indicates that Mg^{2+} loss by hepatocytes is the result of decrease in cellular ATP concentrations,[20,21] which is consistent with magnesium deficiency being characterized by markedly lower Mg^{2+} content in the mitochondria and cytoplasm, the two main cellular compartments containing both Mg^{2+} and ATP.[22] Chronic alcohol administration results in an impairment of the function of both Na^{+}-dependent and Na^{+}-independent Mg^{2+} transporters (by ~75 %).[23,24] The same defect in PKCε translocation is observed, and the magnesium deficiency is associated with a 17 % decrease in cellular ATP concentration.[23] Patients with liver cirrhosis usually have low body magnesium levels. Since our understanding of the mechanisms involved in magnesium homeostasis has improved, it has been shown that both serum and cellular magnesium levels are significantly lower in cirrhosis patients.[13] In cirrhosis, a reduction in intracellular magnesium content has a negative impact on mitochondrial bioenergetics, which heavily depends on the

appropriate intramitochondrial magnesium concentration.[25,26] When mitochondrial function is impaired, oxidation in the hepatocytes is affected, which is associated with a 17 % reduction in ATP production and hepatocytes damage. The subsequent liver repair process leads to additional fibrosis and worsens the cirrhosis.[13]

Magnesium status is closely linked with liver function and may be related to the aetiology of chronic liver disease. In the liver, mast cells contribute to liver fibrosis;[27] animal studies have shown that low-magnesium diet increases the levels of mRNA known to be expressed by mast cells in the liver and induce the emergence of mast cells around portal triads of the liver in Sprague–Dawley rats.[27] Some study reveals that magnesium deficiency affects cellular metabolism in HepG2 liver cells, RAW264.7 macrophages and HUVECs, and that the modulation of cellular responses to extracellular magnesium deficiency in HUVECs depends on the presence of RAW264.7 cells.[28] Having established that magnesium deficiency can aggravate liver cirrhosis, it is of interest whether magnesium intake could ameliorate this pathology. In vivo studies have shown that magnesium administration can alleviate cirrhosis, with both acetylcysteine magnesium and magnesium lithospermate B (MLB) having similar effects.[29,30] After 8 weeks treatment with acetylcysteine magnesium, TGF-β1, nitric oxide, total (tNOS) and inducible (iNOS) nitric oxide synthase levels were significantly lower in cirrhotic tissue, and hepatic lymphocyte infiltration and formation of pseudo lobuli were alleviated.[31] Magnesium is an enzyme cofactor involved in the DNA repair mechanisms which plays a major role in maintaining genomic stability and fidelity.[13] The relationship between liver cancer and body magnesium content has not been fully established, so whether liver cancer leads to reductions in serum and tissue magnesium concentrations is still unknown. However, it was shown that magnesium supplementation can protect the liver and reduce the morbidity and mortality associated with liver cancer.[32] Magnesium plays a vital role in inhibiting the progression of HBV infection to hepatocellular cancer (HCC). HBV infection remains one of the most frequent cause of HCC in the world.[33,34] Magnesium level is closely linked with liver function. Liver diseases have a prominent effect on body magnesium levels, and magnesium levels in turn influence these disease processes. Magnesium supplementation can not only preserve liver function, but also slow the progression of liver disease, and reduce the mortality associated. Although these findings provide a foundation, there is still a great deal to investigate in this field. Few studies have investigated the relationship between magnesium and HCC or viral hepatitis.

In addition, the reason why magnesium deficiency triggers an inflammatory response is still not fully understood, and no clinical studies have explored the therapeutic effects of magnesium in liver patients. Decreased magnesium levels were also found patients with non-alcoholic fatty liver suggesting that alcoholism cannot be the only cause of hypomagnesaemia in patients with fatty liver. Hypomagnesaemia is not only a laboratory symptom of fatty liver but due to its connection with increased oxidative stress, it might be a risk factor in the progression of fatty liver to steatohepatitis.[35] The suggested inverse association between magnesium intake and significant fibrosis is consistent with previous findings on the association of magnesium intake with fatty liver disease,[36] metabolic syndrome, and insulin resistance.[37,38,39] High intake of magnesium may have reduced odds of having significant liver fibrosis.[40] In conclusion, this review demonstrates the importance of links between magnesium and liver function or disease, and implies that novel therapeutic approaches targeting magnesium may be used to improve liver function in the future. Magnesium should be included in the micronutrients that are given in management of all liver disease patients. Further, we observed the possibility of link between total bilirubin levels and serum magnesium levels in all the patients with liver diseases, and it was noted that there is no correlation between the total bilirubin levels and serum magnesium levels, and is thus a non-significant relationship.

CONCLUSIONS

In our study conducted, patients with liver diseases presented with ascites, lower limb oedema, icterus, and some with hepatic encephalopathy. Majority of them are chronic liver disease, almost all of them had lower serum magnesium levels. The importance of links between magnesium and liver function or disease, implies that novel therapeutic approaches targeting magnesium may be used to improve liver function in the future. Magnesium should be included in the micronutrients that are given in management of all liver diseases patients. The correlation between level of serum magnesium and the total bilirubin levels of all the patients in our study were also studied. Table-1 shows correlation between the level of serum magnesium and total bilirubin in liver disease patients of our study, which reveals negative correlation between them, a non-significant relationship.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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