Magnesium Deficiency and Minimal Hepatic Encephalopathy among Patients with Compensated Liver Cirrhosis

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ABSTRACT: **Background:** Magnesium is an essential intracellular cation. Magnesium deficiency is common in the general population and its prevalence among patients with cirrhosis is even higher. Correlation between serum levels and total body content is poor because most magnesium is intracellular. Minimal hepatic encephalopathy is a subclinical phase of hepatic encephalopathy with no overt symptoms. Cognitive exams can reveal minor changes in coordination, attention, and visuomotor function, whereas language and verbal intelligence are usually relatively spared.

Objectives: To assess the correlation between intracellular and serum magnesium levels and minimal hepatic encephalopathy.

Methods: Outpatients with a diagnosis of compensated liver cirrhosis were enrolled in this randomized, double-blinded study. Patients were recruited for the study from November 2013 to January 2014, and were randomly assigned to a control (placebo) or an interventional (treated with magnesium oxide) group. Serum and intracellular magnesium levels were measured at enrollment and at the end of the study. Cognitive function was assessed by a specialized occupational therapist.

Results: Forty-two patients met the inclusion criteria, 29 of whom were included in this study. Among these, 83% had abnormal cognitive exam results compatible with minimal hepatic encephalopathy. While only 10% had hypomagnesemia, 33.3% had low levels of intracellular magnesium. Initial intracellular and serum magnesium levels positively correlated with cognitive performance.

Conclusions: Magnesium deficiency is common among patients with compensated liver cirrhosis. We found an association between magnesium deficiency and impairment in several cognitive function tests. This finding suggests involvement of magnesium in the pathophysiology of minimal hepatic encephalopathy.

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KEY WORDS: intracellular magnesium, liver cirrhosis, magnesium oxide, magnesium deficiency, minimal hepatic encephalopathy

Magnesium is essential for many intracellular processes and structures in the human body, such as muscle contraction and relaxation, neuronal signal transduction, and conduction of the action potential in the myocardium [1]. Most of the body's magnesium is intracellular and less than 1% of the total is found in serum. Therefore, significant magnesium deficiency might be present even though the serum magnesium level is within normal limits. Magnesium deficiency and hypomagnesemia are not synonymous [1,2].

Body magnesium content is influenced and controlled by many factors. Diet is the main source of magnesium. It is absorbed primarily by the small intestines. Parathyroid hormone, vitamin D, vitamin B6, and triglycerides contribute to its absorption, whereas many other factors such as caffeine, alcohol, and salt impair it [3,4].

The kidneys are a primary site for magnesium regulation, where it is filtered, secreted, and absorbed to maintain adequate equilibrium [2]. Bone is the largest magnesium reservoir in the body. It has an important role in maintaining adequate serum levels by remodeling and releasing magnesium cations when needed [5].

Magnesium deficiency has become common in recent decades [5,6]. Its prevalence ranges from 7%, increasing to 36% in the elderly population and up to 65% in critical care patients [1,7]. Several factors contribute to the increasing prevalence of magnesium deficiency, including poor intake (industrialized Western diet) and iatrogenic factors such as diuretics, which are commonly used in patients with cirrhosis.

Magnesium deficiency is assessed by loading magnesium and measuring excretion or by measuring intracellular magnesium directly [8]. The Energy Dispersive X-Ray Analysis (EXA) test is a simple, non-invasive method used to assess intracellular magnesium in sublingual epithelial cells. It is a diagnostic procedure for measuring dynamic intracellular mineral electrolyte levels, using rapidly metabolizing sublingual epithelial cells under analytical scanning electron microscopy [5,9].

Magnesium deficiency can be clinically asymptomatic, although it is usually expressed initially by personality and

behavioral changes, depression, and even psychosis. As the deficiency worsens, neuromuscular manifestations such as tetany, muscle cramps, tremors, and nystagmus can be seen. Total body magnesium and the rate at which the deficiency develops have an important role in its manifestation [1,10]. Magnesium deficiency has been associated with several systemic conditions, including metabolic syndrome, cerebrovascular diseases, malignancies, bacterial and fungal infections, osteoporosis, and liver cirrhosis [2,4,5,8,11-15].

Several studies demonstrated a higher prevalence of magnesium deficiency in patients with liver cirrhosis compared to the general population [6,10,16,17]. Suggested pathogenesis includes decreased magnesium intake, fat malabsorption, diuretic use, renal tubular acidosis, and increased serum levels of growth hormone and glucagon [17].

Patients with alcoholic liver cirrhosis were found to have decreased muscle mass and strength as well as lower magnesium and potassium content in muscle tissue as compared to an age-matched control group [18,19]. Magnesium levels were found to decrease as the severity of liver disease progressed (according to CHILD score) [18-21], and treatment with spironolactone increased muscle strength and electrolytes [18].

As magnesium is crucial to muscle function, its deficiency could explain the fatigue, muscle weakness, and cramps that characterize many patients with cirrhosis. Indeed, magnesium supplementation is common among patients with or without cirrhosis who have leg cramps.

One purpose of this study was to assess whether other complications of cirrhosis, such as encephalopathy, are related to magnesium deficiency. Hepatic encephalopathy has been linked to hyperammonemia. Its spectrum ranges from minimal hepatic encephalopathy (MHE), without recognizable clinical symptoms, to signs of overt encephalopathy with risk of cerebral edema and death. It manifests as a neuropsychiatric syndrome, which can result in impairment of the sleep-wake cycle, cognition, memory, consciousness, personality changes, motor-sensory abnormalities, and decreased energy levels. It results in diminished quality of life and survival. MHE is a subclinical phase that is diagnosed by cognitive exams and exposes small changes in memory, concentration, intellectual function, and coordination. Patients with MHE show deficits mainly in attention and visuomotor abilities, whereas language and verbal intellect are usually relatively spared. The prevalence of MHE among patients with liver cirrhosis varies from 30% to 84% [22-24].

Since both magnesium deficiency and MHE are common among cirrhotic patients, and due to the critical role of magnesium in neuronal signal transduction, we conducted an interventional trial to evaluate the prevalence of magnesium deficiency and the effect of magnesium supplementation on neuromuscular and neuropsychiatric manifestations among patients with compensated liver cirrhosis.

PATIENTS AND METHODS

Our study was an investigator-initiated, prospective, randomized, double-blinded study. It was approved by the local ethics committee and by the national regulatory authority. Adult outpatients at least 18 years of age with a diagnosis of liver cirrhosis, based on clinical and laboratory characteristics, histology, or non-invasive tests, who did not have overt hepatic encephalopathy and were defined as Child A according to the Child-Pugh classification, were recruited to the study from November 2013 to January 2014. The etiology of liver cirrhosis was diverse and included mainly viral hepatitis B and C and non-alcoholic fatty liver disease.

Exclusion criteria were active cancer, special populations such as pregnant women, individuals with mental retardation, dementia, current treatment with magnesium supplements, and renal failure (CCT lower than 50 ml/min).

After obtaining signed informed consent, patients were randomly divided into an interventional group and a control-placebo group. Patients in the treatment group received a daily dose of 520 mg magnesium oxide, orally. The control group received placebo tablets that looked identical. The patients were examined on three occasions during 8 weeks of follow-up: a first meeting at the beginning of the trial, a second meeting after 1 month to evaluate compliance and possible side-effects, and a third meeting 1 month later. On each occasion, the patients had a thorough physical examination. Blood was drawn for evaluation of liver function, venous plasma ammonia, and plasma magnesium. Intracellular magnesium levels were measured using a buccal mucosal swab at the first and last meetings.

COGNITIVE FUNCTION TESTS

All patients performed four cognitive function tests at the beginning and end of the study:

- Montreal Cognitive Assessment (MoCA):
  The MoCA is a screening tool for individuals with mild cognitive impairment (MCI). The test assesses eight domains of cognitive functioning: attention and concentration, executive functions, memory, naming, visual-constructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points. A score of 26 or above is considered normal.
- Clock completion test (CCT):
  In this test, each patient was asked to draw a clock (a circle) with the hands at 11:10. This time was reported to be most likely to identify neurocognitive disorders. A normal score is 0–3 points and a pathological score is 4–7 points.
  This test assesses executive function.
- Digit span examination:
  The digit span examination is part of short mental test (SMT) developed by Treves and Korczyn. In this test, the patient is asked to follow and repeat a series of 7 num-

bers forwards and backwards. This test evaluates working memory.

- The Lowenstein Occupational Cognitive Assessment (LOTCA):
  As patients with liver cirrhosis are suspected to have impaired visuomotor ability, we used parts of the LOTCA to evaluate these abilities, such as two- and three-dimensional perception.

These tests assess various cognitive abilities, such as abstract thinking, attention and concentration, executive functions, memory, language, visual-constructional skills, conceptual thinking, calculations, and orientation.

In addition, the patients were asked to answer a quality of life questionnaire that included eight parameters including as fatigue level, concentration ability, frequency of muscle cramps, and daily physical performance. The results of each test were compared in the two groups at the end of the trial.

STATISTICAL ANALYSIS

All data are expressed as mean ± standard deviation. Comparisons of the study groups (magnesium treatment and placebo) was performed using one-way analysis of variance (ANOVA) or Kruskal-Wallis non-parametric tests, followed by post hoc comparisons. Pearson's product-moment correlation coefficient or Spearman's rho correlation non-parametric test were used to measure the linear correlation between the two blood measurement variables. Pearson's chi-square test was used to compare two groups in the different groups. $P < 0.05$ were considered significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

STUDY POPULATION

Among 42 patients who met the inclusion criteria, 5 were excluded due to renal failure or active malignancy and 8 patients refused to participate in this randomized controlled trial. A total of 29 patients were recruited and 22 completed the trial, 8 in the interventional group and 14 in the control-placebo group. Demographic data and patient co-morbidities are detailed in Table 1. No significant differences were found among the groups regarding age, race, education, or laboratory parameters at the beginning of the study.

Among the study cohort, 55% had cirrhosis as a result of chronic viral hepatitis [Table 2].

Three patients from the treatment group reported diarrhea and were asked by the study team to stop the treatment. Therefore, they were included in statistical analysis regarding data from the beginning of the study only. They were not included in statistical analysis assessing changes during the study period because they did not complete the follow-up.

Table 1. Patient demographic data and co-morbidities (N=29)

Variable	Magnesium group n=14 (%)	Placebo group n=15 (%)
Age, years	62.07 ± 11.99	61.93 ± 8.28
Male	7 (50)	10 (66.7)
Diabetes mellitus	7 (50)	10 (66.7)
Hypertension	8 (57.1)	8 (53.3)
Dyslipidemia	4 (28.6)	7 (46.7)
Obesity	5 (35.7)	9 (60)
Ischemic heart disease	1 (7.1)	2 (13.3)
Congestive heart failure	1 (7.1)	0
Peripheral vascular disease	1 (7.1)	0

*P values were not significant

Table 2. Etiology of liver cirrhosis (N=29)

Etiology	Magnesium group n=14 (%)	Placebo group n=15 (%)
HBV	1 (7.1)	5 (33.3)
HCV	5 (35.7)	5 (33.3)
NAFLD	5 (35.7)	4 (26.7)
Autoimmune hepatitis	1 (7.1)	0
HIV	1 (7.1)	0
PSC/PBC	1 (7.1)	0
Alcohol abuse	0	1 (6.7)

*P values were not significant

HBV= hepatitis B Virus, HCV =hepatitis C Virus, HIV = human immunodeficiency virus, NAFLD = non alcoholic fatty liver disease, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis

LABORATORY RESULTS

At the beginning of the study, the average serum magnesium level among all study patients was 1.96 ± 0.204 mg/dl (normal range 1.6–2.6 mg/dl); 10% had low serum magnesium levels compatible with mild hypomagnesaemia (1 patient in the intervention group, and 2 in the control group). EXA test results indicated 33.3% had low intracellular magnesium levels (2 in the intervention group, and 6 in the control group).

Average blood and intracellular magnesium levels are shown in Table 3. None of the patients had hypomagnesaemia at the end of the study. Ammonia and creatine phosphokinase (CPK) blood levels in either group did not change significantly during the study.

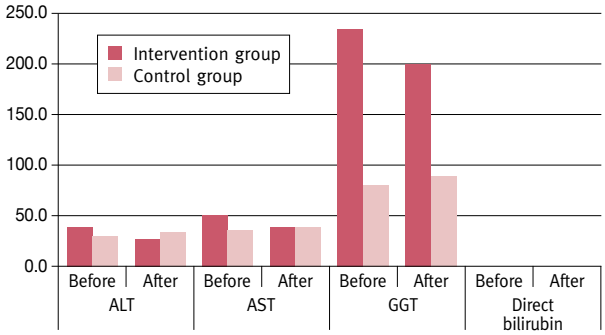
Patients in the treatment group received a daily dose of 520 mg magnesium oxide. We observed an improvement in hepatocellular enzymes during the treatment period, as compared with no significant increase in enzyme levels in the control group [Figure 1]. A similar trend was observed with cholestatic enzymes.

Table 3. Magnesium values and patient symptoms before and after the intervention

Variable	Magnesium group		Placebo group		*P* value
	Before	After	Before	After	
Blood magnesium*	1.97 ± 0.14	2.04 ± 0.13	1.94 ± 0.24	2.01 ± 0.19	NS
Intracellular magnesium*	36.06 ± 3.26	36.68 ± 4.7	34.12 ± 2.23	36.27 ± 1.86	NS
Weakness	30%	10%	33.33%	66.66%	NS
Fatigue	40%	30%	76.00%	73.33%	NS
Sleep disorders	70%	37.50%	53.33%	60%	NS
Loss of appetite	70%	10%	26.67%	23.08%	< 0.05
Muscle cramps	80%	22.20%	84%	58.33%	NS

*average level, in mg/dl
NS = not significant

Figure 1. Change in liver enzymes after magnesium supplementation. A significant decrease in hepatocellular enzymes was observed in the intervention group during the treatment period, compared with no significant increase in enzymes levels in the control group



ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase

COGNITIVE TEST RESULTS

Cognitive test results were abnormal in 83% of patients. As expected, most of the pathology was observed in the visuomotor abilities, whereas language, memory, and intellect were found to be relatively intact. Half of the patients had a pathologic clock completion test. The control group, which had significantly worse clock completion test scores at the beginning of the study as compared with the treatment group ($P = 0.035$), showed greater improvement.

The average MoCA score was 22.38 among all patients before treatment; 66.7% had an abnormal score. All patients showed significant improvement after 3 months (mean increase of 3 points, $P < 0.05$). This improvement caused some test scores, as well as the average test score, to fall into the normal range.

At study initiation, only 22.2% (4 of 18 patients) had a normal long-term memory test. After the intervention, patients in the treatment group had significantly better scores than the placebo group did (average of 4.17 vs. 2.75, respectively, $P = 0.031$).

Both groups demonstrated improvement in recall memory after 8 weeks, without statistical significance (mean 7.2–8.3 after 3 months, $P = 0.428$ in the treatment group, compared to an average increase of 7.3–7.8 after 8 weeks, $P = 0.294$ in the control group).

Correlation between initial laboratory parameters and cognitive performance was evaluated for all participants. As the intracellular magnesium level increased, performance in most cognitive tasks improved. Some of the correlations were statistically significantly and others showed only a trend. A significant correlation was observed between intracellular magnesium and the digit span task ($P = 0.007$). Serum magnesium level was also significantly correlated to the LOTCA test ($P = 0.05$).

FATIGUE AND MUSCLE CRAMPS

Muscle cramps were experienced by 83% of the study population. At the beginning of the study, 70% of the patients reported fatigue and muscle weakness and 66.6% reported sleep disturbances. Patients treated with magnesium reported improvement in fatigue during the study, while the control group did not experience such an improvement (they had increased fatigue at the end), but the change was not statistically significant ($P = 0.37$).

Patients treated with magnesium reported a significant improvement in appetite ($P = 0.024$). Improvement in the severity and frequency of muscle cramps was not significant ($P = 0.438$ and 0.483, respectively).

We found a positive correlation between muscle weakness and sleep disorders ($P = 0.006$) and decreased concentration ability ($P = 0.006$). Frequency and severity of muscle cramps were also positively correlated to muscle weakness ($P = 0.02$ and 0.001, respectively).

DISCUSSION

This randomized, controlled study aimed to assess prevalence of magnesium deficiency among a small cohort of subjects with compensated liver cirrhosis, and to find a possible correlation between magnesium deficiency and cirrhosis complications, such as MHE and muscle cramps.

MHE has an impact on the quality of life and functional status of patients with liver cirrhosis. MHE was found in about 85% of the patients at the beginning of the study according to cognitive testing. This prevalence is acceptable compared to the literature, in which the prevalence is 30–84% [23]. This difference could be due to the selection bias of a single center trial and overestimation of cognitive pathologies due to a single, specialized occupational therapist who assessed all the patients.

Hypomagnesemia is not a rare phenomenon among patients with compensated liver cirrhosis (we found a prevalence of 10%). Measuring the intracellular magnesium revealed even

higher prevalence of magnesium deficiency (about one-third of patients). This prevalence should be confirmed in a larger study, but could be explained by iatrogenic factors that characterize this population, such as the use of certain medications. In our study, 20.7% of the patients were treated by diuretics, such as furosemide, and 13.8% were treated with proton pump inhibitors, which can interfere with magnesium absorption. These medications can cause a possible underestimation of the magnesium effect on the study population because they interfere with magnesium metabolism. In addition, standard deviations were greater in the treatment group compared to the placebo group, which could also explain the nonsignificant increase in the intracellular magnesium of the treatment group. Magnesium plasma levels did not change in either group.

The improvement in hepatocellular enzymes during the treatment period in the magnesium group might indicate an anti-inflammatory effect of magnesium. This finding should be evaluated in future studies.

In the treatment group, many patients reported a trend toward improvement in fatigue and in the severity and the frequency of muscle cramps. This improvement, along with the insignificant decrease in the CPK level in the treatment group was not observed in the placebo group. Taken together, these findings could support the involvement of magnesium in the pathogenesis of myopathy in cirrhosis, compatible with the findings of Aagaard and colleagues [19]. As magnesium is an intracellular ion involved in adenosine triphosphate and energy generation, depletion of total body magnesium could explain some of the common clinical features of cirrhosis, such as fatigue and muscle cramps.

A possible association between magnesium levels and the cognitive function tests is extremely important from a therapeutic point of view. Both serum and intracellular magnesium were correlated with concentration and visuomotor ability, but due to the limitations of our small, short-term study, we could not show a causative effect of magnesium on these tests. The cognitive test results of many patients from the two groups improved during the study. This finding can be partially explained by a learning process of repeating the same tests at an interval of only a few weeks. This improvement was observed in all patients and masked some of the differences between the two groups at the end of the study. To overcome this effect, we referred to the study population as a whole. We assessed the correlation between the cognitive tests and the magnesium levels that were taken at the first study visit. When observing all the cirrhotic patients as one group, we found important correlations between the laboratory parameters and cognitive function.

This study also revealed the important issue of subclinical cognitive deficits, which can progress without proper screening and treatment [24]. Exercising cognitive tasks might contribute to preservation of function before definitive treatment is found, such as a cure for HCV or liver transplantation.

We hypothesized that by replenishing the magnesium stores in a population with high prevalence of magnesium deficiency, cognitive impairment might improve, but we could not prove this in this small trial.

Although this study was designed as a randomized, double-blind study, it had several limitations, including a small number of patients, single-center selection bias, and heterogeneity of years of education among the study population.

Other issues to consider in the future are dosage and formulation of magnesium to maximize absorption and minimize side effects. Whether magnesium deficiency aggravates cognitive dysfunction in cirrhotic patients or has its own role in the pathogenesis of minimal hepatic encephalopathy remains to be explored. The therapeutic role of magnesium in cirrhotic patients should be determined in larger studies.

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Capsule

Ribavirin is effective as post exposure prophylaxis for Crimean-Congo hemorrhagic fever

Ergonul et al. performed a systematic review and meta-analysis on the effectiveness of ribavirin use for the prevention of infection and death of healthcare workers exposed to patients with Crimean-Congo hemorrhagic fever virus (CCHFV) infection. Splashes with blood or bodily fluids (odds ratio [OR] 4.2), being a nurse or physician (OR 2.1), and treating patients who died from CCHFV infection (OR 3.8) were associated with healthcare workers acquiring CCHFV infection; 7% of the workers who received postexposure prophylaxis (PEP) with ribavirin and 89% of those who did not became infected. PEP with ribavirin reduced the odds of infection (OR 0.01, 95% confidence interval [95%CI] 0–0.03), and ribavirin use ≤ 48 hours after symptom onset reduced the odds of death (OR 0.03, 95%CI 0–0.58). The odds of death increased 2.4-fold every day without ribavirin treatment. Ribavirin should be recommended as PEP and early treatment for workers at medium-to-high risk for CCHFV infection.

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Eitan Israeli

Capsule

A turbulent way to make platelets

Donations from volunteers are the only source of blood for transfusions. But blood components such as platelets have a shelf life of only 5 days, and alternative sources of platelets are in demand. By visualizing fluorescently tagged megakaryocytes (precursor cells of platelets) in transgenic mice, **Ito** et al. demonstrated that highly turbulent blood flow is a determining factor of platelet production from megakaryocytes. Turbulence triggered the production of thrombopoietic factors from megakaryocytes, which, along with shear stress, stimulated platelet release. By using a turbulence-controllable bioreactor, functionally viable platelets could be generated from megakaryocytes derived from human-induced pluripotent stem cells at a quantity that satisfies clinical-scale demand, suggesting the possibility of de novo platelet production as an alternative to acquiring platelets through blood donations.

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Eitan Israeli

Capsule

Zika in the testes: a Trojan horse

Zika virus (ZIKV) is a mosquito-borne flavivirus that can also be sexually transmitted. Although people infected with ZIKV are often asymptomatic, there is an association between ZIKV infection in pregnant women and severe birth defects in their children. **Matusali** and colleagues showed that ZIKV can replicate for several days in testicular tissue explants. ZIKV infects testicular somatic cells, germ cells, and spermatozoa, and its presence has been detected in semen samples from ZIKV-infected patients. Despite induction of antiviral genes, no overt inflammatory response was observed, and testicular morphology and hormone production remained unaffected. Apparently, ZIKV remains quiescent in the testes. This phenomenon may explain asymptomatic disease transmission and offer a possible target for antiviral drugs.

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