Serum & muscle magnesium in Indians with cirrhosis of liver

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Magnesium status of Indian patients with cirrhosis of liver (alcoholic and non alcoholic) and the role of low magnesium in neuromuscular and neuropsychiatric manifestations of chronic liver disease were evaluated in 76 male cirrhotics (alcoholic 37, aged 48 ± 11 yr, non alcoholic 39, aged 47 ± 12 yr) and 37 male controls (aged 49 ± 11 yr). Serum magnesium levels were similar in the 3 groups studied. Muscle magnesium in both groups of cirrhotics were significantly lower than in controls (alcoholic cirrhosis 33.77 ± 16.85; non alcoholic cirrhosis 37.93 ± 18.86 and controls 70.52 ± 6.49 mEq/kg fat free dry mass; \( P < 0.001 \)). Multiple regression analysis comparing muscle magnesium with clinical and biochemical parameters in cirrhosis showed that hepatic encephalopathy was associated significantly and independently with low muscle magnesium (Beta = −0.313; \( P = 0.01 \)). These results indicate that patients with cirrhosis have significantly lower muscle magnesium than controls and suggests that low muscle magnesium may be a factor associated with or precipitating hepatic encephalopathy.

Key words  Hepatic encephalopathy - Indian patients - muscle magnesium - serum magnesium

Hypomagnesaemia has been demonstrated in cirrhosis of the liver and is reported to be due to several mechanisms like deficient intake, excess urinary loss and deficient absorption\(^1\)\(^-\)\(^4\). As Indians and orientals have a higher dietary intake of magnesium as compared to caucasians\(^5\); it is possible that the magnesium status of Indian cirrhotics may be different from that of Western cirrhotics. Severe magnesium deficiency has also been shown in acute and chronic alcoholism\(^3\)\(^-\)\(^6\). Hence, it is reasonable to expect a greater degree of magnesium deficiency in alcoholic cirrhosis as compared to non alcoholic cirrhosis.

Serum magnesium level is commonly used in clinical practice to demonstrate magnesium deficiency. Studies have however shown that there is no correlation between serum and intracellular magnesium\(^5\)\(^,\)\(^7\). The superiority of intracellular magnesium over serum magnesium in determining magnesium status of patients has also been demonstrated\(^8\).

As neuromuscular and neuropsychiatric symptoms are seen in magnesium deficiency\(^4\)\(^,\)\(^7\)\(^,\)\(^9\), it has been hypothesised that hypomagnesaemia may play a role in the neuropsychiatric and neuromuscular manifestations of liver disease. There are however no studies demonstrating this association.

The aims of the present study therefore were to (i) evaluate magnesium status (serum and muscle) of Indian patients with cirrhosis of liver; (ii) determine if there is a difference in magnesium status between alcoholic and non alcoholic cirrhosis; and (iii) to evaluate the role of low serum/muscle magnesium in neuromuscular and neuropsychiatric manifestations of liver disease.
Material & Methods

Subjects: Male patients (76) who were admitted to the Christian Medical College Hospital, Vellore, Tamil Nadu during January 1990 to December 1991 and diagnosed to have cirrhosis of the liver and portal hypertension by standard criteria were randomly selected and studied. This group was divided into 2 subgroups:

(i) Alcoholic cirrhosis - 37 patients. Alcoholic cirrhosis was diagnosed if patients had cirrhosis of the liver, consumed more than 60 g alcohol per day for a period exceeding five years and had no other etiology for cirrhosis detected on work up.

(ii) Non alcoholic cirrhosis - 39 patients. Non alcoholic cirrhosis was diagnosed if patients had cirrhosis of the liver and either did not consume alcohol or consumed less than 20 g per day for a period less than five years.

Thirty seven male patients aged 49 ± 11 yr admitted for elective surgery like herniorrhaphy and interval appendicectomy formed the control group. None of them were malnourished, consumed alcohol or had evidence of liver disease.

Patients were excluded from the study if they had diabetes mellitus; renal failure (serum creatinine > 1.4 mg/dl; diarrhoea during the preceding one month; aminoglycoside antibiotics or magnesium containing antacids or laxatives during the preceding one month; or diuretics for more than 7 days during the preceding one month.

Design: After admission, patients were interviewed and clinically examined. They were followed up for 7 days during which symptoms and signs of hypomagnesaemia as well as neuromuscular and neuropsychiatric manifestations of liver disease were assessed. During this period standard investigations to determine diagnosis of cirrhosis and portal hypertension, its etiology and complications were performed. Liver biopsy was not performed in most of the patients with cirrhosis either because it was contraindicated (ascites, prolonged prothrombin time) or because patient did not give consent. Serum magnesium and muscle biopsy to determine muscle magnesium were also performed.

Laboratory methods: After 12 h overnight fast, blood was drawn by yepuncture without venous stasis. Estimation of serum calcium, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), serum albumin, alkaline phosphatase and creatinine were done on a Boehringer Mannheim Hitachi-911 clinical automated analyzer (Germany) using standard techniques. Serum potassium was measured using an ion selective electrode from Radiometer, Denmark. Serum magnesium was measured by atomic absorption spectroscopy. Corrected serum magnesium (mmol/l) was estimated using the formula: Measured serum magnesium + 0.005 (40-albumin) g/l.

After a minimum 4 h of bed rest, muscle biopsy from the right quadriceps muscle was performed after local infiltration of 2 per cent xylocaine. A piece of muscle approximately 0.5 g was obtained. This was immediately sealed, frozen and stored for analysis.

Muscle magnesium was estimated by the method described by Allen et al. Briefly, the biopsied muscle was carefully dried in a crucible for 24 h at 100°C, the specimens were incinerated at 450°C for 6-8 h, residue dissolved in 0.75 per cent EDTA solution and magnesium content estimated by atomic absorption spectrometry (Perkins Elmer 2380, Norwalk, Connecticut, USA) after necessary dilution.

All patients gave informed consent for muscle biopsy.

Statistical analysis: Univariate analysis was done using SPSS/PC (Statistical package for social sciences). Multiple regression analysis was then performed using those variables which were significant on univariate analysis as well as other clinically important variables using the same statistical package. To compare the 3 study groups Student’s ‘t’-test was used. Correlations were studied using Pearson’s correlation coefficient.
Table I. Clinical characteristics, biochemical parameters and severity of liver disease in alcoholic and non-alcoholic cirrhotics and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls n = 37</th>
<th>Alcoholic cirrhosis n =37</th>
<th>Non-alcoholic cirrhosis n =39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 11</td>
<td>48 ± 11</td>
<td>47 ± 12</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>21 (43.2)</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td>Oedema</td>
<td>0</td>
<td>31 (83.8)</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td>Ascites</td>
<td>0</td>
<td>34 (91.9)</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.1 ± 0.3</td>
<td>3.3 ± 4.5&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2.7 ± 1.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Albumin (g%)</td>
<td>3.9 ± 0.6</td>
<td>2.5 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alanine transaminase (U/l)</td>
<td>32 ± 11</td>
<td>64 ± 52&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57 ± 42&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aspartate transaminase (U/l)</td>
<td>34 ± 12</td>
<td>52 ± 34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61 ± 40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>105 ± 17</td>
<td>122 ± 39&lt;sup&gt;a&lt;/sup&gt;</td>
<td>117 ± 39&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)</td>
<td>8.4 ± 0.6</td>
<td>9.1 ± 0.6</td>
<td>9.2 ± 0.7</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4.5 ± 1.7</td>
<td>3.4 ± 0.6&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>3.1 ± 0.38&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prothrombin index (%)</td>
<td>100</td>
<td>71 ± 11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71 ± 10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.3</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Childs’ Score*</td>
<td>A</td>
<td>2 (5.4)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>15 (40.5)</td>
<td>16 (41.0)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>20 (54.1)</td>
<td>18 (46.2)</td>
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</table>

Values are mean ± SD; Figures in parentheses are the percentages

*Pugh's modification of Child's criteria<sup>22</sup>

<sup>a</sup>P < 0.01 as compared to controls; and<sup>b</sup>non alcoholic cirrhosis

Results

Patients with alcoholic cirrhosis and non-alcoholic cirrhosis were grossly similar in their clinical and biochemical profile as well as severity of liver disease (Table I).

The corrected serum and muscle magnesium levels in the 3 groups studied are shown in Table II. Serum magnesium in patients with alcoholic and non-alcoholic cirrhosis were similar and to controls. Severity of liver disease as assessed by Pugh's modification of Child's criteria<sup>22</sup> did not correlate with corrected serum magnesium (r = 0.1432). There was no correlation between serum albumin and serum magnesium (r = 0.064).

Muscle magnesium levels in alcoholic and non-alcoholic cirrhotics were significantly lower than in controls (P < 0.001). However, muscle magnesium was similar in alcoholic and non-alcoholic cirrhotics. Severity of liver disease (Childs criteria) did not correlate with muscle magnesium (r = 0.0642). There was no correlation between serum and muscle magnesium (r = 0.31).

Univariate analysis of patients with cirrhosis comparing muscle magnesium with clinical characteristics and biochemical parameters showed that spider naevi (49.2%; P = 0.06) and hepatic encephalopathy (55.6%; P = 0.03) were more common in patients with low muscle magnesium. A multiple regression analysis
Table II. Serum and muscle magnesium in cirrhotics and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls n = 37</th>
<th>Alcoholic cirrhosis n = 37</th>
<th>Non-alcoholic cirrhosis n = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum magnesium (mmol/l)</td>
<td>1.23 ± 0.34</td>
<td>0.98 ± 0.33</td>
<td>1.22 ± 0.35</td>
</tr>
<tr>
<td></td>
<td>(0.81 – 1.62)</td>
<td>(0.57 – 1.64)</td>
<td>(0.51 – 1.67)</td>
</tr>
<tr>
<td>Muscle magnesium</td>
<td>70.52 ± 6.49</td>
<td>33.77 ± 16.85*</td>
<td>37.93 ± 18.86*</td>
</tr>
<tr>
<td>(mEq/kg fat free dry mass)</td>
<td>(40.64 – 78.34)</td>
<td>(16.24 – 76.14)</td>
<td>(16.92 – 71.98)</td>
</tr>
</tbody>
</table>

Values are mean ± SD, Figures in parantheses are the range

*P < 0.001 as compared to controls

using low muscle magnesium (≤ 57 mEq/kg fat free dry muscle) as the dependant variable and oedema, spider naevi, ascitis, cramps, delirium, Child’s score and hepatic encephalopathy as the independent variables showed that hepatic encephalopathy was significantly and independently associated with low muscle magnesium (Beta = −0.313; P = 0.01).

Discussion

Serum magnesium is often used as a measure to assess body magnesium status. This has been shown to be unreliable as intracellular and serum magnesium do not correlate7,8,23. Muscle magnesium has been shown to be a reliable and convenient method for evaluating intracellular magnesium status7,23. The magnesium contents of muscles biopsied from different sites have been shown to be similar24. Though the dietary intake of magnesium in Indians is significantly higher than in Western subjects5, the present study shows that magnesium status of Indians is similar to subjects from developed countries7,25.

Corrected serum magnesium levels in cirrhosis in the present study were similar to controls. These results are similar to that found by Lim and Jacob23, but different from earlier studies where hypomagnesaemia has been reported in patients with cirrhosis. Lim and Jacob23, found that the serum ultrafilterable levels of magnesium were normal in spite of low serum magnesium and suggested that the hypomagnesaemia reported in cirrhosis in earlier studies could have been due to failure to correct for hypoalbuminaemia. Our data however showed no correlation between serum magnesium and serum albumin in patients with cirrhosis (r = 0.06) to support this hypothesis. This could have been due to the narrow range of values for serum albumin in the present study. Studies on starvation of obese subjects have shown low skeletal muscle magnesium with normal serum magnesium26. Catabolic release of intracellular magnesium may be responsible for maintaining normal serum levels in these patients. It is possible that similar mechanisms could have contributed to normal serum magnesium levels observed in cirrhosis in the present study.

Muscle magnesium levels in the present study were significantly lower in patients with cirrhosis as compared to controls. These results are similar to that of Lim and Jacob23 and show significant intracellular magnesium deficiency in patients with cirrhosis. Decreased intake due to the loss of appetite and prolonged illness as well as the increased faecal loss due to malabsorption may contribute to the magnesium deficiency in cirrhosis4,6. Increased urinary loss of magnesium can occur secondary to hyperaldosteronism4 or use of drugs like diuretics and aminoglycosides4,6. It is unlikely that these drugs were responsible for the low muscle magnesium seen in the present study as patients with history of intake of these drugs were excluded. Secondary hyperaldosteronism is usually seen in cirrhotic patients with ascites. If hyperaldosteronism was an important cause for excess loss of magnesium in urine, one would expect a correlation between low magnesium levels and presence of ascites. However, no such correlation
was found suggesting that hyperaldosteronism may not be a major factor responsible for low muscle magnesium in the present study.

Patients with alcoholic and non-alcoholic cirrhosis were grossly similar in their clinical and biochemical parameters as well as severity of liver disease. Severe hypomagnesaemia has been demonstrated in acute and chronic alcoholism. So it is reasonable to expect patients with alcoholic cirrhosis to be more magnesium deficient than non-alcoholic cirrhosis. However in the present study serum and muscle magnesium levels were similar in both alcoholic and non-alcoholic cirrhosis. A possible explanation for this finding is that most of the patients with alcoholic cirrhosis had stopped alcohol for more than 3 months prior to the study.

Neuromuscular and neuropsychiatric symptoms are common clinical manifestations of magnesium deficiency. So, it has been hypothesised that there may be an association between low serum/muscle magnesium levels and neuromuscular and neuropsychiatric manifestations of liver disease. Though neuromuscular and neuropsychiatric symptoms of liver disease like muscle weakness, tremors, cramps, paraesthesias, apathy, agitation, confusion, delirium and nystagmus were more common among patients with low muscle magnesium, this was not statistically significant. Multiple regression analysis showed that muscle magnesium levels had a significant negative linear trend with the presence of hepatic encephalopathy. This suggests that low muscle magnesium may be a factor associated with or precipitating hepatic encephalopathy. Further studies are required to confirm this association.

References


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