**ASSOCIATION OF VITAMIN B12 AND FOLIC ACID WITH CHRONIC LIVER DISEASE**

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**ABSTRACT**

**Introduction:** CLD is an important cause of morbidity and mortality. Alcohol abuse is the most common etiology of CLD in the population. In liver cirrhosis patients, the distortions of hepatic parenchyma result in the progressive loss of the hepatic form and function, compromising, in varied degrees, the nutritional state and body homeostasis of the subjects. Chronic alcoholism is known to interfere with one-carbon metabolism, for which vitamin B12 and folic acid serve as coenzymes. Folate is probably the most commonly affected vitamin in alcoholism. Vitamin B-12 deficiency, assessed as low circulating concentrations, is thought to be less common in chronic alcoholics, probably because of large hepatic stores.

**Material and Methods:** This study was conducted on 50 clinically diagnosed patients of chronic liver disease and 50 age and sex matched healthy persons taken as controls. The detailed history of patient regarding age, sex and related information was recorded, after taking the informed written consent from the patients. Approx. 3ml of venous blood sample was taken under all aseptic conditions for investigations. The samples were taken and analyzed for Vitamin B12 and Folic acid levels. Statistical analysis was done.

**Results:** It was observed that vitamin B12 levels were increased significantly in study group than controls showing a highly significant relation with p<0.001. Serum folic acid levels were decreased in study group when compared with controls.

**Conclusion:** It was observed that vitamin B12 levels were increased and folic acid levels were decreased in patients with chronic liver disease.

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**INTRODUCTION**

Although liver disease is stereotypically linked to alcohol or drugs, but there are many other causes of liver disease which include Chronic Hepatitis(classified as viral hepatitis, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), autoimmune liver disease, Wilson disease), Fatty Liver, Liver Cirrhosis(viral cirrhosis, alcoholic cirrhosis), Hepatocellular Carcinoma(HCC). CLD shows impaired liver function, an increased intrahepatic resistance (portal hypertension) and the development of Hepatocellular carcinoma.[¹] CLD is an important cause of morbidity and mortality. Alcohol abuse is the most common etiology of CLD in the preventable cause of death. Although there are various causes of death among liver disease alcoholism stands out as a significant cause of mortality. As the disease progresses, portal pressure increases and liver function decreases, resulting in the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy and jaundice. [²] In liver cirrhosis patients, the distortions of hepatic parenchyma result in the progressive loss of the hepatic form.[³] Methionine synthase, is a methyltransferase enzyme, which uses the MeB₁₂ to transfer a methyl group from 5-methyltetrahydrofolate to homocysteine, thereby generating tetrahydrofolate (THF) and methionine. This functionality is lost in vitamin B₁₂ deficiency, resulting in an increased homocysteine level and the trapping of folate as 5-methyl THF, from which THF (the active form of folate) cannot be recovered and body THF pool is reduced.[⁴] The deficiency of vitamin B₁₂ in the periphery may be due to its leaking out from the damaged hepatic cells. Increases in vitamin B₁₂ in cirrhotic and liver mass patients could be due to hepatocellular damage. A cellular leakage of vitamin B₁₂ with a subsequent intracellular vitamin B₁₂ deficiency has been proposed for liver cirrhosis.[⁵] In hepatocellular damage, vitamin B₁₂ binding and storage is disrupted and causes vitamin B₁₂ to leak out of the liver into the circulation.[⁶] Excessive alcohol intake lasting longer than two weeks can decrease vitamin B₁₂ absorption from the gastrointestinal tract.

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[¹]Chronic alcohol consumption is the third leading preventable cause of death. Although there are various causes of death among liver disease alcoholism stands out as a significant cause of mortality. As the disease progresses, portal pressure increases and liver function decreases, resulting in the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy and jaundice. [²] In liver cirrhosis patients, the distortions of hepatic parenchyma result in the progressive loss of the hepatic form.[³] Methionine synthase, is a methyltransferase enzyme, which uses the MeB₁₂ to transfer a methyl group from 5-methyltetrahydrofolate to homocysteine, thereby generating tetrahydrofolate (THF) and methionine. This functionality is lost in vitamin B₁₂ deficiency, resulting in an increased homocysteine level and the trapping of folate as 5-methyl THF, from which THF (the active form of folate) cannot be recovered and body THF pool is reduced.[⁴] The deficiency of vitamin B₁₂ in the periphery may be due to its leaking out from the damaged hepatic cells. Increases in vitamin B₁₂ in cirrhotic and liver mass patients could be due to hepatocellular damage. A cellular leakage of vitamin B₁₂ with a subsequent intracellular vitamin B₁₂ deficiency has been proposed for liver cirrhosis.[⁵] In hepatocellular damage, vitamin B₁₂ binding and storage is disrupted and causes vitamin B₁₂ to leak out of the liver into the circulation.[⁶] Excessive alcohol intake lasting longer than two weeks can decrease vitamin B₁₂ absorption from the gastrointestinal tract.
Chronic liver disease especially ALD is associated with folate deficiency, which is the result of reduced dietary folate intake, intestinal malabsorption and increased urinary folate excretion. Folate deficiency favors the progression of liver disease through mechanisms that include its effects on methionine metabolism.[7] Chronic alcoholism is known to interfere with one-carbon metabolism, for which vitamin B12 and folic acid serve as coenzymes. Folate is probably the most commonly affected vitamin in alcoholism. Vitamin B12 deficiency, assessed as low circulating concentrations, is thought to be less common in chronic alcoholics, probably because of large hepatic stores.[8] Alcohol consumption can deplete the levels of circulating folate specifically, highlighting that a sufficient volume of THF will not be present to act as a co-factor within the reaction.[8] Severe alcoholic liver disease involves leakage of total B12 from liver tissue into the plasma which initiates highly elevated B12 levels in plasma. Chronic consumption of alcohol impairs the uptake and retention of vitamin B12 by the liver and other peripheral tissues.[10] Serum vitamin B12 and serum folate in ALD patients showed that serum folate values were lower compared to healthy subjects and B12 values tend to be higher in patients compared to healthy subjects. There was emerging evidence indicating that ethanol induced alterations in hepatic methionine metabolism caused by folate and vitamin B12 deficiency which played a central role in the pathogenesis of alcoholic liver disease.[11] The ingestion of alcohol lowers serum folate levels and impairs haematological recovery, which is possibly through a catabolic effect of alcohol metabolism on the folate. Low serum folate levels have been shown in more than two thirds of sessional drinkers.[12]

In this study Folic acid along with Vitamin B12 are vital parameters which can indicate the initialization of underlying chronic liver disease. So attempts were made to interrelate these for finding relevant results.

**Experimental Section**

This study was conducted in the Department of Biochemistry on total of 50 clinically diagnosed patients of chronic liver disease. The control group comprised of 50 age and sex matched healthy persons free from any systemic illness. Detailed history of patient regarding age, sex and related information was recorded, after taking the informed written consent from the patients. Approx. 3ml of venous blood sample was taken under all aseptic conditions for investigations. The sample was allowed to clot and centrifuged at 3000 rpm for 10 minutes and analyzed for all the investigations. Folic acid and vitamin B12 tests were performed on fully automated chemiluminescence, Access 2 (Beckman Coulter).

**Reference values**

- Vitamin B12: 180-914 pg/mL.[13]
- Folic Acid: 2.3 to greater than 24.8 ng/mL.[14]

Statistical analysis was done using SPSS version 16. All the tests were 2 tailed and the p value < 0.05 was considered significant.

**RESULTS**

The samples were analysed for Vitamin B12 and Folic acid in patients of chronic liver disease and following results were obtained.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>N</th>
<th>Mean±S.D</th>
<th>t value</th>
<th>p value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12</td>
<td>Study Group</td>
<td>50</td>
<td>1436.16±263.77</td>
<td>23.31</td>
<td>0.000</td>
<td>Highly Significant</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>50</td>
<td>303.82±219.98</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data displayed in the above table states that levels of Vitamin B12 were increased significantly in study group than controls. This showed a highly significant relation with p<0.001.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>N</th>
<th>Mean±S.D</th>
<th>t value</th>
<th>p value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic Acid</td>
<td>Study Group</td>
<td>50</td>
<td>12.87±5.40</td>
<td>6.58</td>
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</tr>
<tr>
<td></td>
<td>Control group</td>
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<td>6.07±3.38</td>
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</table>

As seen in the above table, serum folic acid levels were decreased in study group when compared with controls. And there was significant difference in the levels of folic acid in both groups (p<0.001).

**DISCUSSION**

According to the present study, vitamin B12 levels were higher in the chronic liver disease patients with a mean value of 1436.16± 263.77 pg/ml in study group and 303.82±219.98 pg/ml in controls (p=0.000). Another parameter estimated was folic acid, which decreased in the patients with chronic liver disease. The mean value of folic acid was 6.075±3.38 ng/dl in the study group and 12.87±5.40 ng/dl in controls which was highly significant with p<0.05. In the study, Vitamin B12 levels were found to be increased in the patients due to the fact that the storage functioning of the liver is disrupted in liver damage which causes leakage of vitamin B12 from the hepatic cells and causing increased Vitamin B12 in the circulation. Furthermore, folate deficiency was attributed to combinations of poor diet, impaired folate absorption, and increased urinary folate excretion.

A prospective observational study done by Muro N et al.[15] observed that cirrhotic patients presented plasma levels of vitamin B12 higher 1151 ± 568pg/ml in study group and 440 ± 133pg/ml in controls (p <0.05). There are fewer studies to determine plasma levels of vitamin B12 in patients with chronic liver disease and even less than these levels differ depending on the etiology and also supported the same fact of the study that plasma folate levels were low 6.68 ± 2.74ng / ml in patients(p <0.05) as compared to8.57 ± 3.8ng / ml in controls. Over two thirds of the chronic alcoholics have low levels of folic acid. Kanazawa S et al.[16] observed that alcoholics had low levels of vitamin B12 in the liver and high in plasma. These findings suggest how retention cobalamin occurs in peripheral tissues, followed by an accumulation of this vitamin in plasma.

**CONCLUSIONS**

Serum vitamin B12 tends to increase with increasing hepatocellular damage and Folate deficiency favors the progression of liver disease through mechanisms that include its effects on methionine metabolism.
References

16. Kanazawa S, Herbert V. Total corrinoid, cobalamin (vitamin B12), and cobalamin analogue levels may be normal in serum despite cobalamin depletion in liver in patients with alcoholism. Lab Invest 1985;53:108-10

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