CLINICAL STUDY

Serum magnesium levels in patients with alcoholic and non-alcoholic fatty liver

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Abstract

Introduction: **Magnesium is currently a subject of major interest in biology and medicine. Magnesium is intimately involved in over 300 enzymatic reactions. particularly in processes involving the formation and utilization of ATP. It is known that alcoholism is connected with hypomagnesemia. There are also several studies describing the disorders of magnesium balance in patients with liver diseases.**
The aim of study: **was to investigate the serum magnesium levels in patients with liver steatosis. We compared the magnesium levels in patients with non-alcoholic and alcoholic fatty liver to estimate if alcoholism is the only cause of magnesium disorders or if also liver function disorders play any role in the development of magnesium dysbalance in patients with liver steatosis.**
Patients and methods: **The studied group consisted of 44 patients with hepatic steatosis (25 non-alcoholic and 19 alcoholic). The control group consisted of 57 healthy subjects. Magnesium levels were assayed by atomic absorption spectrometry.**
Results: **Serum magnesium levels were significantly decreased in patients with alcoholic (0.67 ± 0.10 vs 1.02 ± 0.11 mmol.l^{-1}) and also in patients with non-alcoholic liver steatosis (0.65 ± 0.14 vs 1.02 ± 0.11 mmol.l^{-1}). There were also moderately increased activities of aminotransferases and gamma-glutamyltransferase. Plasma triacylglycerols were increased in both studied groups. Albumin and prealbumin levels were not changed in comparison to the control group. There was a slight increase in plasma levels of immunoglobulin A and immunoglobulin G.**
Conclusions: **The results of our study showed hypomagnesemia in both studied groups. Decreased magnesium levels found also in patients with non-alcoholic fatty liver suggest that alcoholism cannot be the only cause of hypomagnesemia in patients with fatty liver. Hypomagnesemia 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 *(Tab. 3, Ref. 19)*.**
Key words: liver, fatty liver, liver disease, magnesium, hypomagnesemia, steatohepatitis.

Magnesium is currently a subject of major interest in biology and medicine. It is the fourth most abundant cation in the body and second most prevalent intracellular cation. Magnesium is intimately involved in over 300 enzymatic reactions, particularly in processes involving the formation and utilization of ATP (Elin, 1994). It also has an important endocrine function and is required for protein synthesis. An accumulating line of evidence strongly suggests that magnesium plays an essential role in the function of cell membrane sodium-potassium ATPase pump (Flatman and Lew, 1981). Magnesium is an obligate ion that is essential for the activation of many enzymes. Included are enzymes involved in glucose metabolism, fatty acid synthesis and breakdown, and DNA and protein metabolism. In addition, magnesium is required for the activity of adenylate cyclase, which transmits extracellular hormonal signals to the intracellular apparatus.

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Tab. 1. Serum magnesium levels and hepatic enzymes activities in controls and in patients with fatty liver.

Parameter	Mg mmol/l	ALT µcat/l	AST µcat/l	CHE µcat/l	GMT µcat/l
controls	1.02±0.11	0.38±0.07	0.31±0.09	61.2±12	0.30±0.16
non-alcoholic	0.65±0.14	0.74±0.21	0.67±0.15	73.3±19	0.56±0.41
fatty liver	p<0.001	p<0.001	p<0.01	p<0.01	p<0.01
alcoholic	0.67±0.10	0.81±0.15	0.68±0.17	69.5±18	1.28±0.68
fatty liver	p<0.001	p<0.001	p<0.01	NS	p<0.001

Results are given as mean±SD, Mg – magnesium, ALT – alanine aminotransferase, AST – aspartate aminotransferase, GMT – gamma-glutamyltransferase, CHE – cholinesterase, statistical difference from controls, NS – not significant

Magnesium is primarily an intracellular cation. The serum magnesium comprises less than 1 % of the total body magnesium. Magnesium is either bound to protein, complexed to anions or free. Unbound magnesium, i.e. ionized magnesium is regarded as the biologically active form (Elin, 1987). A growing body of evidence links the altered status of ionized magnesium to many pathophysiological states and diseases.

Since the first report in 1936 by Cline and Coleman, numerous studies have been published describing a marked deficiency of total magnesium in chronic alcoholism. There are several studies describing the disorders of magnesium balance in patients with liver diseases (Long et al, 1978, Saha et al, 1998, Koivisto et al, 2002).

In the present study we investigated the serum magnesium levels in patients with liver steatosis. We compared the magnesium levels in patients with non-alcoholic and alcoholic fatty liver to estimate if alcoholism is the only cause of magnesium disorders or if also liver function disorders play any role in the development of magnesium dysbalance in patients with liver steatosis.

Patients and methods

Subjects. The study group consisted of 44 patients with liver steatosis (non-alcoholic liver steatosis – 25 patients, aged 35–64 years, alcoholic liver steatosis – 19 patients, aged 36–57 years). The diagnosis was confirmed histologically. Control group consisted of 57 healthy subjects (mainly blood donors), aged 18–62 years. For the determination of biochemical parameters, samples of antecubital venous blood were drawn.

Biochemical analysis. The total serum magnesium was determined by atomic absorption spectrometry (Varian AA-475, Varian Techtron Pty. Ltd., Australia).

The activity of cholinesterase was assayed by the kinetic method of Knedel and Bottger (1967) using butyrylthiocholine iodide as substrate at 25 °C. Serum prealbumin,albumin, transferrin, apoprotein A and immunoglobulins concentrations were determined by electroimmunodiffusion (Laurell, 1966) using a monospecific antisera. Cholesterol and triacylglycerols were determined by enzymatic methods (Cholesterol DST-P and Triglyceridy DST-P, DOT diagnostics s.r.o., Praha, Czech republic). HDL-cholesterol was determined after the precipitation of LDL+VLDL by magnesium chloride/phosphotungstic acid (HDL-C, Boehringer Mannheim GmbH, Germany). LDL-cholesterol was calculated according to Friedewald et al (1972).

Statistical analysis. Values are given as mean±SD. When the data presented the Gaussian distribution, parametric tests were used (Student's t-test for differentiating of avarages and Pearson's correlation coefficient). When data did not have the Gaussian distribution, non-parametric tests were used (Wilcoxon's test for comparing of populations and Spearman's correlation coefficient) and *p* values less than 0.05 were regarded as statistically significant. Statistical analyses were performed using Statgraphics Plus statistical software Version 5.0.

Results

The determination of total magnesium levels in controls and patients with fatty liver showed, that serum concentrations of magnesium were significantly decreased in both groups of patients with fatty liver (Tab. 1). The comparison of magnesium levels in sera of patients with alcoholic and non-alcoholic liver steatosis showed no difference between these two groups. The determination of serum activities of hepatic enzymes showed moderately but significantly increased activities of both aminotransferases in sera of patients with liver steatosis (Tab. 1). There was no significant difference between activities of aminotransferases in sera of both groups of patients with liver steatosis. The serum activity of cholinesterase was significantly increased in patients with non-alcoholic fatty liver. The activity of cholinesterase was slightly increased also in patients with alcoholic fatty liver, but this change was not statistically significant. The activity of gamma-glutamyltransferase was significantly increased in both groups of patients with liver steatosis. The activity of gamma-glutamyltransferase was significantly higher in sera of patients with alcoholic fatty liver than in patients with non-alcoholic fatty liver.

Investigation of blood lipid parameters – triacylglycerols and total cholesterol – showed a statistically significant increase in triacylglycerols in sera of patients with alcoholic and also in those with non-alcoholic liver steatosis (Tab. 2). The levels of total cholesterol in patients with fatty liver did not differ statistically from cholesterol levels in the control group. The determination of concentrations of cholesterol fractions – HDL-cholesterol and LDL-cholesterol – showed a slight but significant decrease in HDL-cholesterol level in patients with alcoholic liver steatosis.

Tab. 2. Lipid parameters in sera of controls and patients with fatty liver.

Parameter	TGL mmol/l	CHOL mmol/l	HDL-C mmol/l	LDL-C mmol/l	apoA g/l
controls	0.75±0.25	4.48±0.99	1.39±0.19	2.74±0.42	0.30±0.16
non-alcoholic	1.52±0.73	5.05±1.15	1.23±0.26	3.21±0.87	1.43±0.27
fatty liver	p<0.001	NS	NS	NS	NS
alcoholic	2.18±1.30	5.51±1.17	1.08±0.11	3.56±1.10	1.28±0.08
fatty liver	p<0.001	NS	p<0.05	NS	p<0.01

Results are given as mean±SD, TGL – triacylglycerols, CHOL – total cholesterol, HDL-C – HDL-cholesterol, LDL-C – LDL-cholesterol, apoA – apoprotein A, statistical difference from controls, NS – not significant

Tab. 3. Plasma protein levels in controls and patients with fatty liver.

Parameter	ALB g/l	PREA mg/l	TRF g/l	IgG g/l	IgA g/l
controls	40.4±2.5	304±38	3.07±0.33	12.8±1.6	2.0±0.68
non-alcoholic	41.0±2.3	285±49	3.07±0.42	15.4±3.8	2.6±0.70
fatty liver	NS	NS	NS	p<0.01	p<0.01
alcoholic	41.6±2.6	313±57	2.83±0.42	16.3±4.5	3.0±0.87
fatty liver	NS	NS	p<0.05	p<0.01	p<0.001

Results are given as mean±SD, ALB – albumin, PREA – prealbumin, TRF – transferin, IgA – immunoglobulin A, IgG – immunoglobulin G, statistical difference from controls, NS – not significant

HDL-cholesterol in patients with non-alcoholic fatty liver showed no significant change when compared to HDL-cholesterol level in controls. The levels of LDL-cholesterol were not significantly different in both studied groups of patients with fatty liver when compared to the control group. Adequately to the changes in HDL-cholesterol levels also the levels of apoprotein A were changed.

The investigation of plasma proteins showed no changes in levels of albumin and prealbumin in patients with liver steatosis (Tab. 3). The levels of both studied immunoglobulins – IgG and IgA – were significantly increased in sera of both groups of patients. Plasma levels of transferrin were slightly but significantly decreased in patients with alcoholic liver steatosis. Transferrin levels in patients with non-alcoholic fatty liver were practically the same as in the control group.

Discussion

Hepatic steatosis is a very common finding in clinical practice, especially in an outpatient setting, and is very often associated with slight alteration of either aminotransferases or gamma-glutamyltransferase, or both (Bellentani and Tiribelli, 2001). The results of our study confirmed changes in activities of aminotransferases and gamma-glutamyltransferase described in sera of patients with fatty liver.

Fatty liver is mainly associated with those pathological conditions that are connected with increased substrate supply of free fatty acids: particularly in obesity, hyperlipoproteinemia, diabetes and alcohol. All these conditions are associated with an increase in hepatic uptake of fatty acids, usually originating from lipolysis of triacylglycerols stored in adipose tissue. In some cases there may also be a decrease in mitochondrial β-oxidation of long-chain fatty acids and/or decreased hepatic secretion of triacylglycerols as very low density lipoproteins. Fat accumulation in the liver is the earliest and the most common response to alcohol. Fatty liver can be induced by either acute or chronic administration of alcohol both in laboratory animals and man (Lieber, 1985).

The determination of total serum magnesium level in our patients with alcoholic and non-alcoholic fatty liver showed hypomagnesemia in both studied groups. Magnesium deficiency is associated with diverse effects, mainly with cardiovascular, neurological, endocrine and muscular symptoms. It is not surprising that magnesium levels were decreased in patients with alcoholic fatty liver because the connection of hypomagnesemia with alcoholism has been known for long time (Flink, 1986, Shane and Flink, 1990). Several mechanisms associated with alcoholism contribute to magnesium deficiency, including urinary Mg wastage, malnutrition, gastrointestinal losses, phosphate deficiency, acidosis/alcalosis, vitamin D deficiency and free fatty acidemia associated with alcohol withdrawal (Flink, 1986). Thirty percent of all alcoholics had hypomagnesemia during the first 24-48 hours after the admission to hospital (Sullivan et al, 1969). The fact that we found decreased magnesium levels not only in patients with alcoholic hepatic steatosis but also in patients with non-alcoholic hepatic steatosis suggests that alcoholism cannot be the only cause of hypomagnesemia in patients with fatty liver and that in the latter patients also other factors participate in the pathogenesis of hypomagnesemia. Our results are in agreement with those of Schulte (1978), who also found hypomagnesemia in patients with chronic non-alcoholic liver diseases. Koivisto et al (2002) described hypomagnesemia in patients with liver cirrhosis. The factors that might cause hypomagnesemia in patients with liver diseases include (1) poor absorption of magnesium in

distal jejunum, (2) enhanced urinary magnesium excretion due to high serum levels of aldosterone, (3) administration of magnesiuric diuretics (furosemide), (4) decreased plasma level of albumin and finally (5) poor intake of magnesium due to malnutrition (Cohen, 1985, Koivisto et al, 2002).

Our patients suffered only from hepatic steatosis which is a relatively benign liver disorder. Hyperaldosteronism was not present, and these patients were not treated with diuretics. According to our results, serum albumin levels were not decreased in both studied groups of patients and therefore hypoalbuminemia cannot be the cause of the decrease in total serum magnesium levels in patients with fatty liver.

One of the possible factors participating in the development of hypomagnesemia in our patients might be the decrease in magnesium absorption. Despite the fact that hepatic steatosis is a relatively benign liver disorder it might be connected with some disorders of liver functions, e.g. decreased secretion of bile acids. The presence of slight cholestasis suggests increased activities of alkaline phosphatase and gamma-glutamyltransferase in sera of patients with fatty liver. We found also increased activities of gamma-glutamyltransferase in our patients with fatty liver. Disorder in the secretion of bile acids might have resulted in malabsorption of lipids in these patients. Increased amounts of fatty acids in the intestinal lumen form insoluble soaps with Mg^{2+}. This leads to the loss of magnesium from both, dietary and endogenous sources.

It is important to notice that hypomagnesemia is not only one of laboratory symptoms of hepatic steatosis but it might be one of factors participating in the progression of fatty liver to steatohepatitis and cirrhosis. It is known, that Mg-deficiency increases the susceptibility of plasma triacylglycerol-rich lipoproteins and tissues to lipoperoxidation (Kramer et al, 1994, Gueux et al, 1995), but the precise mechanism by which Mg deficiency can potentiate oxidative injury remains to be determined. The net effect of fatty acid accumulation in the liver is simple steatosis, but unless there is an additional factor that initiates hepatocellular injury and inflammation there is no chronic liver disease and, in particular, no fibrosis. One of risk factors participating in the progression of fatty liver to steatohepatitis is oxidative stress. Due to increased lipoperoxidation, hypomagnesemia and Mg deficiency might participate in the progression of fatty liver to steatohepatitis and then to cirrhosis.

Conclusions

The results of our study showed hypomagnesemia in sera of patients with alcoholic and non-alcoholic hepatic steatosis. Decreased magnesium levels found also in patients with non-alcoholic fatty liver suggest that alcoholism cannot be the only cause of hypomagnesemia and that there must be still some other factors participating in the development of hypomagnesemia in these patients. Hypomagnesemia 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.

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