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Effect of Hepatoprotective Agent Liv.52 on Nutrition Parameters in Hemodialysis Patients

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ABSTRACT

Background and Aims

Malnutrition, inflammation and atherosclerosis are leading causes of morbidity and mortality in uremic patients. Objective of the study was to evaluate the effect of Liv.52 on nutritional parameters in patients on hemodialysis.

Methods

Sixty seven patients on hemodialysis (mean age 52.5 ± 10.4 years, dialysis duration 5.5 ± 3.1 years) were tested. First group included 42 patients on Liv.52, 6 tablets a day. Among these 42 patients, there were 16 patients who were hepatitis C virus antibody-positive (anti-HCV Ab+) (38%), without clinical or laboratory signs of active hepatic lesions. The control group of 25 patients was not significantly different in age, sex and type of dialysis treatment. At the beginning, and at the end of a 6 month period, serum urea, creatinine, hemoglobin, albumins, triglyceride and cholesterol levels were monitored in both groups. The adequacy of dialysis (Kt/V), normalized protein catabolic rate (nPCR), clinical and subjective parameters of protein-energy status (body mass index, "dry" body weight), midarm muscle circumference (MAMC), tricep skinfold thickness (TSF), and in the tested group, the subjective global nutrition assessment – SGNA were also monitored. Parameter values were given in average values. Differences between groups and within the groups, before and after the therapy, were tested with t-test and the Kolmogorov-Smirnov and Wilcoxon rank tests.

Results

At the start of the study, the first group had significantly lower cholesterol values than the control group (4.9 ± 1.2 vs 5.8 ± 1.5 mmol/l; $p<0.05$). There was no significant difference in serum albumin, urea, creatinine, hemoglobin, triglycerides, BMI, MAMC and TSF. At the end of the 6 month period, the tested group showed highly significant increases in albumin (35.6 ± 2.7 vs 41.7 ± 2.5 g/l; $p<0.01$) and triglyceride levels (1.8 ± 0.7 vs 2.4 ± 1.2 mmol/l; $p<0.01$), increase of cholesterol level (4.9 ± 1.2 vs 5.3 ± 0.4 mmol/l; $p<0.05$) and a decrease in urea level (32.6 ± 6.6 vs 26.8 ± 4.7 mmol/l; $p<0.01$). Patients showed significant increase

of “dry” body weight (63.3 ± 9.3 vs 64.5 ± 8.8 kg; $p<0.05$) and body mass index (22.4 ± 2.4 vs 23.0 ± 2.0 kg/m^2; $p<0.01$), as well as MAMC (22.0 ± 2.8 vs 25.5 ± 3.4 mm; $p<0.001$) and TSF (10.3 ± 3.7 vs 14.1 ± 5.3 mm; $p<0.01$). Within the control group, there was a slight increase in MAMC, though not significant (22.6 ± 2.6 vs 23.1 ± 2.4 mm; $p<0.05$) and TSF (9.8 ± 3.9 vs 10.4 ± 3.7) was not significant either. Triglyceride levels significantly increased in the control group (2.4 ± 1.1 vs 3.1 ± 1.5 mmol/l; $p<0.05$), while the rest of the biochemical parameters and body mass index did not change significantly. According to the subjective global nutritional assessment, improvement was achieved in 71% of the patients with Liv.52 treatment.

Conclusion
The obtained results show that the use of Liv.52 as an additional protective remedy in the therapy of malnutrition patients on dialysis is justified.

Keywords
Hemodialysis, malnutrition, Subjective Global Nutrition Assessment, Liv.52

INTRODUCTION:

Malnutrition is common among patients on maintenance hemodialysis. A 40% prevalence of malnutrition was found in patients with advanced renal failure at the beginning of dialysis treatment. Signs of malnutrition are observed in 10-70% of hemodialysis patients and in 18-51% of patients on continuous ambulatory peritoneal dialysis[1,2].

Malnutrition increases the risk of serious infections. It has been proposed that malnutrition may also contribute to cardiovascular disease that in turn is the main cause of patient mortality. Various mechanisms have been proposed[3].

Malnutrition *per se* may markedly reduce myocardial mass, the content of myofibrils and other functional elements. Low albumin levels may influence the generation of lipoproteins associated with atherosclerosis as shown *in vitro* in human hepatoma cell-line. Accumulation of asymmetric dimethyl-L-arginine (ADMA), which is an endogenous competitive inhibitor of nitric oxide (NO) synthase, may inhibit NO-induced vasodilation, thus predisposing to hypertension and cardiovascular disease. However, it has been reported more recently that ADMA levels are higher in end stage renal disease than in controls but always lower than the concentrations that induce vasoconstriction *in vivo.*

The protective effect of Liv.52 is well-known. It is a preparation, which contains extracts of several plants used in the management of liver disorders. It has been used for a long-time in India and the rest of the world for the treatment of liver damage of named etiology and malnutrition, mostly in children where it is used as an anabolic[4-7] agent and as an agent, which stimulates appetite and improves general condition[8-10].

The aim of the study was to evaluate the influence of Liv.52 as a hepatroprotective agent[11,12] with its effect on albumin synthesis, and on nutritional parameters in hemodialysis patients.

MATERIAL AND METHODS

Sixty seven patients on a time-bound program of hemodialysis were included in this prospective, case-controlled pilot study. They were divided in two groups. The first group consisted of 42 patients (27 males, 15 females, mean age 57.2 ± 9.6 years, and average dialysis duration 6.7 ± 3.9 years), mean values of dialysis adequacy measurement (Kt/V) 1.02 ± 0.24, nPCR 1.27 ± 0.31, the body mass index (BMI), 22.4 ± 2.4 kg/m^2 (Table 1). These patients were being treated with Liv.52, 6 tablets a day, divided in three daily doses, one hour before meals, for six months. Liv.52 tablet contain: *Capparis spinosa* 65 mg, *Cichorium intybus* 65 mg, *Solanum nigrum* 32 mg, *Cassia occidentalis* 16 mg, *Terminalia arjuna* 32 mg, *Achillea millefolium* 16 mg, *Tamarix gallica* 16 mg and Mandur bhasma (Ferric oxide calx) 33 mg. The control group consisted of 25 patients (14 men and 11 women, the mean age 50.3 ± 9.6 years, average dialysis duration 6.6 ± 4.1 years, mean values Kt/V 1.09 ± 0.28, nPCR 1.20 ± 0.29, BMI 23.0 ± 2.9 kg/m^2) who were not treated with Liv.52 (Table 1).

Table 1: Demographics and clinical characteristics of patient population

	Treated patients	Untreated patients	*P*
N	42	25	-
Age (years)	57.2 ± 9.6	50.3 ± 9.6	NS
Duration of dialysis (years)	6.7 ± 3.9	6.6 ± 4.1	NS
Kt/V	1.02 ± 0.24	1.09 ± 0.28	NS
BMI (kg/m^2)	22.4 ± 2.4	23.0 ± 2.9	NS
MAMC (mm)	22.0 ± 2.8	22.6 ± 2.6	NS
TSF (mm)	10.3 ± 3.7	9.8 ± 3.9	NS
Anti HCV Ab+ve patients	16 (38%)	8 (32%)	-

No single method is available in order to evaluate nutritional status in hemodialysis patients. Most authors agree that a multiparametric evaluation, which includes assessment of dietary intake, body weight, skinfold thickness and arm muscle circumference, serum albumin, serum prealbumin, serum transferrin and subjective global assessment is appropriate.

Tested and control group did not differ significantly in age, sex and dialysis duration, effectiveness of dialysis and BMI. Most common causes of renal failure were chronic glomerulonephritis and pyelonephritis (Table 2). All together, there were 24 anti-HCV Ab+ve patients (in tested group 16, in control group 8), but none of them showed clinical or laboratory signs of active liver lesions (Table 1). The following biochemical parameters in serum were monitored in all patients at the start of the study and after 6 months: hemoglobin, urea, creatinine, total proteins, albumin, triglyceride, cholesterol (enzymatic method). Blood samples were taken before dialysis, in the middle of

Table 2: Causes of end-stage renal disease (ESRD)

Chronic glomerulonephritis	50%
Chronic pyelonephritis	17%
Hypertension	14%
Balkan nephropathy	10%
Polycystic kidney disease	9%

the dialysis week. The midarm muscle circumference (MAMC) was derived from triceps skinfold thickness (TSF) and midarm circumference (MAC) measured in the fistula free arm of the patients: MAMC = MAC – (p x TSF). Subjective global nutrition assessment (SGNA) was used to evaluate total protein-energy status in patients treated with Liv.52. Patients were interviewed at the beginning and at the end of the study. The SGNA included 6 subjective parameters, three based on anamnestic data obtained from patients about body weight loss, incidence of anorexia and vomitus, and three based on physician's evaluation of loss of muscle mass, presence of edema and loss of subcutaneous fat tissue. On the basis of these 6 parameters, each patient got a score which displayed nutritive status thus: 1 = normal, 2 = mild malnutrition, 3 = moderate malnutrition and 4 = severe malnutrition. After hemodialysis, we established "dry" body weight (optimal body weight after a hemodialysis session) and body mass index (BMI).

Statistical analysis

Parameters values were given in mean values. Significance of the difference between the groups and within the group (before and after the therapy), were evaluated with t-test and the Kolmogorov-Smirnov and Wilcoxon rank tests.

RESULTS

At the start of the study, the group on Liv.52 therapy had statistically lower cholesterol values than the control group (4.9 ± 1.2 vs 5.8 ± 1.5 mmol/l; $p<0.05$). There were no statistically significant differences in albumin (35.6 ± 2.7 vs 35.2 ± 3.6 g/l; $p>0.05$), urea (32.6 ± 6.6 vs 25.6 ± 4.4 mmol/l; $p>0.05$), creatinine (941 ± 161 vs 927 ± 219 mcmol/l; $p>0.05$), triglyceride values (1.8 ± 0.7 vs 2.31 ± 1.1 mmol/l; $p>0.05$), hemoglobin (8.8 ± 0.9 vs 8.9 ± 1.2 g/l, $p>0.05$), BMI (22.4 ± 2.4 vs 23.0 ± 2.9 kg/m^2; $p>0.05$), MAMC (22.0 ± 2.8 vs 22.6 ± 2.6 mm; $p>0.05$) and TSF (9.8 ± 3.9 vs 10.4 ± 3.7). At the end of the six month period, there was a statistically significant increase in albumin level (35.6 ± 2.7 vs 41.7 ± 2.5 g/l; $p<0.01$), highly significant increase in triglyceride level (1.8 ± 0.7 vs 2.4 ± 1.2 mmol/l; $p<0.01$), significant increase in cholesterol level (4.9 ± 1.2 vs 5.3 ± 0.4 mmol/l; $p<0.05$), and decrease in urea level (32.6 ± 6.6 vs 26.8 ± 4.7 mmol/l; $p<0.01$) in the tested group (Table 3). Hemoglobin values did not change significantly (8.8 ± 0.9 vs 9.3 ± 1.9 g/l); neither did creatinine (941 ± 161 vs 968 ± 288 mcmol/l; $p>0.05$). MAMC (22.0 ± 2.8 vs 25.5 ± 3.4 mm;

Table 3: Biochemical and anthropometrics parameters of nutritional status in treated patients at the beginning (0 months) and at the end of the treatment period (6 months)

	0 month	6 months	*P*
Urea (mmol/l)	32.6 ± 6.6	26.8 ± 4.7	<0.01
Creatinine (mcmol/l)	941 ± 161	968 ± 288	NS
Albumin (g/l)	35.6 ± 2.7	41.7 ± 2.5	<0.01
Triglycerides (mmol/l)	1.8 ± 0.7	2.4 ± 1.2	<0.01
Cholesterol (mmol/l)	4.9 ± 1.2	5.3 ± 0.4	<0.05
Hemoglobin (g/l)	8.8 ± 0.9	9.3 ± 1.9	NS
BMI (kg/m^2)	22.4 ± 2.4	23.0 ± 2.0	<0.01
'Dry' body weight (kg)	63.3 ± 9.3	64.5 ± 8.8	<0.05
MAMC (mm)	22.0 ± 2.8	25.5 ± 3.4	<0.001
TSF (mm)	10.3 ± 3.7	14.1 ± 5.3	<0.01
Kt/V	1.20 ± 0.24	1.34 ± 0.14	<0.01

p<0.001) and TSF (10.3 ± 3.7 vs 14.1 ±5.3 mm; p<0.01) significantly increased. Within the control group, there was a statistically significant increase of triglyceride (2.3 ± 1.1 vs 3.1 ± 1.5 mmol/l; p<0.05), while the rest of the parameters didn't show statistically significant changes (albumins 35.2 ± 3.6 vs 35.4 ± 2.9 g/l; cholesterol 5.8 ± 1.5 vs 5.5 ± 1.3 mmol/l; urea 25.6 ± 4.4 vs 26.4 ± 4.7 mmol/l, creatinine 927 ± 219 vs 997 ± 198 mcmol/l; hemoglobin 8.9 ± 1.2 vs 9.1 ± 1.7 g/l). There was no statistically significant change in "dry" body weight (64.9 ± 11.9 vs 65.2 ± 10.5 kg), MAMC (22.6 ± 2.6 vs 23.1 ± 2.4 mm; p>0.05), BMI (23.0 ± 2.9 vs 23.1 ± 2.8 kg/m^2) and TSF (9.8 ± 3.9 vs 10.4 ± 3.7) in the control group (Table 4). At the end of the six month period, Kt/V was significantly different in the therapeutic group (1.2 ± 0.4 vs 1.34 ± 0.14; p<0.01) (Table 3). nPCR improved in both groups, but not significantly (in treated group 1.27 ± 0.31 vs 1.38 ± 0.38; in control group 1.20 ± 0.29 vs 1.23 ± 0.23).

Table 4: Biochemical and anthropometrics parameters of nutritional status in untreated patients at the beginning (0 months) and at the end of the treatment period (6 months)

	0 month	6 months	*P*
Urea (mmol/l)	25.6 ± 4.4	26.4 ± 4.7	NS
Creatinine (mcmol/l)	927 ± 219	997 ± 198	NS
Albumin (g/l)	35.2 ± 3.6	35.4 ± 2.9	NS
Triglycerides (mmol/l)	2.3 ± 1.1	3.1 ± 1.5	<0.05
Cholesterol (mmol/l)	5.8 ± 1.5	5.5 ± 1.3	NS
Hemoglobin (g/l)	8.9 ± 1.2	9.1 ±1.7	NS
BMI (kg/m^2)	23.0 ± 2.9	23.1 ± 2.8	NS
'Dry' body weight (kg)	64.9 ± 1.9	65.2 ± 10.5	NS
MAMC (mm)	22.6 ± 2.6	23.1 ± 2.4	<0.05
TSF (mm)	9.8 ±3.9	10.4 ± 3.7	NS
Kt/V	1.09 ± 0.28	1.14 ± 0.25	NS

In therapeutic group at the beginning of the study, 44% of the patients were moderately malnourished and 3% severely according to SGNA, BMI and serum albumins. At the end of the study, the treated group had registered a significant increase in patients "dry" body weight (63.3 ± 9.3 vs 64.5 ± 8.8 kg; p<0.05) and BMI (22.4 ± 2.4 vs 23.0 ± 2.0 kg/m^2; p<0.01). According to the individual score of subjective discomforts (nausea, bad appetite, tiredness, fatigue), which was formed within SGNA, after six months of therapy, the number of patients with severe discomfort decreased from 24% to 5%, and patients with moderate discomfort from 48% to 31%, while the number of patients with mild discomforts changed from 29% at the beginning to 65% at the end of therapy. Statistically, there was a highly significant improvement with 59% of patients, 39% did not show any changes and only 2% showed deterioration, the cause for which cannot be specified.

Considering all parameters mentioned above, total improvement was achieved with 71% of patients, 21% showed no changes and deterioration happened with 5%. There were no registered undesirable side effects of the medicine.

DISCUSSION

The protective effect of Liv.52, a multiplant agent, was established several decades ago on liver damage induced by ethanol[13-16]. Results obtained in these studies show that treatment

with Liv.52 can prevent enzyme activity increase of gamma-glutamic transpeptidase. In this way lipid peroxidation process, which ethanol accelerates, is reduced and activity of antioxidative enzymes – superoxydismutase and glutation peroxidase is increased. The hepatoprotective nature of this agent has been proved and it can be explained with inhibition of lipid peroxidation.

Our results show that Liv.52 is effective additional medicine for malnourished patients on hemodialysis. A significant increase of biochemical nutritive markers, albumin and lipid fractions (triglyceride and cholesterol), was evident with improved synthesis with appetite improvement and reduced nausea which is usually common in this population because of the increase of uremic toxins. The significantly decreased urea level in serum after therapy can probably in part be explained with a decrease in catabolism. Biochemical results in the control group, before and after six months did not change significantly except for the increase of serum triglyceride. A positive effect on body weight and BMI in patients who were on therapy with Liv.52 during the 6 month period has been registered.

Several factors could interfere with reactions to Liv.52 therapy in our patients. In patients with liver lesions (anti HCV Ab+ patients), the most common indication for the use of this additional therapy, there is a possible stimulative effect on regeneratory liver capacity, further improving the patient's status and nutritive parameters. It is known that patients on dialysis take a lot of medicaments because of the complexity of their treatment, so Liv.52 can have a protective role here.

Severe anorexia and malnutrition are certainly the main reasons for including Liv.52 therapy with this population, though cardial status and signs of inflammation can change the influence of Liv.52 on the patients' general condition.

Malnutrition is an important determinant of comorbidity and mortality in dialysis patients. These results suggest that intake of Liv.52, as a protective agent, had significant beneficial impact on nutritional parameters and even more on SGNA. Among the numerous studies exploring the effect of Liv.52 we could not find any investigations done in malnourished hemodialysis patients. In conclusion, obtained results show that the use of Liv.52 as an additional protective medicine is justified in therapy of malnourished patients on chronic hemodialysis programme.

CONCLUSION

The nutritional management of dialysis patients now appears of the first importance. A regular nutritional assessment is necessary in order to verify the diet adequacy and to detect malnutrition. Nutritional therapy in dialysis patients was shown to be able to improve nutritional status.

Identification of malnutrition in hemodialysis patients may essentially rely on subjective global assessment and measurement of serum albumin levels. Strategies to prevent or treat

malnutrition include standard (dietary counseling, oral food supplements, intradialytic parenteral nutrition) and more experimental (appetite stimulants, growth hormone, IGF-1) therapies.

Liv.52 may be included as a supportive therapy in the management of malnutrition associated with chronic hemodialysis.

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