Prevalence of fat-soluble vitamin (A, D, and E) and zinc deficiency in patients with cirrhosis being assessed for liver transplantation

A. Teriaky[1], M. Mosli[3], N. Chandok[2], B. Al-Judaibi[1,4,5], P. Marotta[1], K. Qumosani[1]

(1) Department of Medicine, Division of Gastroenterology and Hepatology, Western University and London Health Sciences Centre, London, Ontario, Canada ; (2) Department of Medicine, Division of Gastroenterology, William Osler Health System, Brampton, Ontario, Canada ; (3) Department of Medicine, King Abdulaziz University, Jeddah, KSA ; (4) Department of Medicine, King Saud University, Riyadh, KSA ; (5) Department of Medicine, Division of Gastroenterology, University of Rochester City, NY, USA.

Abstract

Purpose : **To evaluate the prevalence of fat-soluble vitamin (A, D, and E) and zinc deficiency in patients with cirrhosis being assessed for liver transplantation and the correlations between vitamin deficiencies, nutritional markers, and severity of liver disease.**

Methods : **This is a single centre retrospective study. Serum vitamin A, D, E, and zinc levels were collected in adult patients being assessed for liver transplantation between January and July 2012. Patient and liver disease demographics, nutritional markers, Child-Pugh score, and MELD-Na score were collected. Fisher's exact test and multiple variable logistic regression was used for statistical analysis.**

Results : **A total of 109 adult patients were assessed for liver transplantation during the 6-month period. The mean patient age was 54 ± 10 years and 66% were males. Mean BMI was 27 ± 6 kg/m², pre-albumin was 0.10 ± 0.07 g/L, albumin was 33 ± 6 g/L, total bilirubin was 48 ± 61 mmol/L, MELD-Na score was 16 ± 5 (range 6-33), and 15% had hepatocellular carcinoma. The Child-Pugh score was A in 29%, B in 54%, and C in 17%. The causes of liver disease were hepatitis C in 36%, alcohol in 20%, non-alcoholic fatty liver disease in 17%, and other in 27%. The mean vitamin A level was 0.88 ± 0.86 umol/L, D was 69 ± 52 nmol/L, E was 24 ± 17 umol/L, and zinc was 477 ± 145 ug/L. Vitamin A deficiency was prevalent in 77%, D in 63%, E in 37%, and zinc in 84%. On multiple variable analysis, low albumin (OR = 0.78, 95% CI = 0.65-0.94, p = 0.0069) was a predictor of vitamin A deficiency ; cholestatic liver enzyme elevation (OR = 3.53, 95%CI = 1.40-8.89, p = 0.0073) and low albumin (OR = 0.83, 95%CI = 0.73-0.94, p = 0.0032) were predictors of vitamin D deficiency ; low albumin (OR = 0.85, 95% CI = 0.74-0.97, p = 0.015) was a predictor of vitamin E deficiency ; and age (OR = 0.83, 95% CI = 0.72-0.96, p = 0.012), low albumin (OR = 0.59, 95% CI = 0.42-0.84, p = 0.0036), and high MELD-Na (1.43, 95% CI = 1.05-1.94, p = 0.021) were predictors of zinc deficiency. Vitamin A (p = 0.0034), D (p = 0.020), E (p = 0.012), and zinc (p<0.001) deficiency correlated with a higher Child-Pugh.**

Conclusion : **Low albumin was a recurrent predictor of fat-soluble vitamin (A, D, and E) and zinc deficiency while other predictors varied depending on the vitamin or mineral. Further studies need to be conducted on fat-soluble vitamin and zinc supplementation in deficient patients with cirrhosis to assess clinical outcomes.** (Acta gastroenterol. belg., **2017**, 80, **237-241**).

Key words : Fat-soluble vitamin, vitamin A, vitamin D, vitamin E, zinc, deficiency, cirrhosis, liver transplantation

Introduction

Malnutrition is commonly associated with advanced liver disease and its severity worsens with the progression of liver disease (1). The prevalence of malnutrition in patients with cirrhosis is high, ranging from 53-90% (1-3). Malnutrition plays a significant role in liver related morbidity and mortality (4-6). This makes screening patients for malnutrition an important part of the clinical assessment. This has historically included the subjective global assessment and anthropometric parameters (7). Sarcopenia has been more recently used as a nutritional measure, which correlates with mortality (8,9). Malnutrition in cirrhotics can be attributed to a variety of factors including : decreased nutrient intake, hypermetabolic state, alterations in macronutrient and micronutrient metabolism, malabsorption, and medication adverse effects (10-12). Malnutrition in turn leads to vitamin and mineral deficiency, which can manifest with various clinical sequelae. Thus, it is important to not only identify malnutrition, but vitamin and mineral deficiency in order to correct the underlying problem.

Fat-soluble vitamin (FSV) absorption requires bile acids to form micelles, which are absorbed by enterocytes into the circulation. The liver is an important storage center for these vitamins and plays an active role in their metabolism.

Chronic cholestasis occurs in patients with cirrhosis, which is believed to limit absorption of these fat-soluble vitamins and possibly lead to deficiencies (13). The sequelae of vitamin A deficiency includes visual impairment, dry skin, and a weakened immune system (14). Vitamin D deficiency is associated with muscle weakness and metabolic bone diseases such as osteopenia, osteoporosis, and osteomalacia (15,16). Vitamin E deficiency may cause neuromuscular disorders, anemia, and visual disturbances (17). Prior studies have been limited and inconclusive in determining an association between fat-soluble vitamin deficiency and the severity of liver disease (13-17).

Zinc is the second most prevalent trace mineral in the human body and plays an important role in cellular

Correspondence to : Karim Qumosani MD, FRCPC, Department of Medicine, Division of Gastroenterology and Hepatology, London Health Sciences Centre,University Hospital, Room ALL-126, 339 Windermere Road, London, Ontario, Canada, N6A 5A5, Email : karim.qumosani@lhsc.on.ca

Submission date : 23/03/2016
Acceptance date : 24/10/2016

growth, catalytic reactions, and immune regulation. Zinc is absorbed in the gastrointestinal tract by transporters on enterocytes (18). The liver plays an essential part in zinc homeostasis with zinc also being necessary for appropriate liver function. Zinc deficiency has been implicated in liver disease (19). If malnutrition plays an adverse role on outcomes in cirrhotics, then determination of these deficiencies and correction may be helpful.

The purpose of this study is to evaluate the prevalence of FSV (A, D, and E) and zinc deficiency in patients with cirrhosis being assessed for liver transplantation (LT) and to determine if a correlation exists between vitamin and zinc deficiencies, nutritional markers, and severity of liver disease.

Methods

This is a retrospective study that was conducted at London Health Sciences Centre (LHSC), a tertiary care and LT centre, in London, Ontario, Canada. The research ethics board at our institute approved this study. All patients presenting for a LT assessment between January and June 2012 would undergo FSV and zinc serum level analysis in addition to the standard preliminary investigations performed at our institute. These investigations included : a complete blood count, comprehensive metabolic panel, coagulation studies, viral hepatitis serology, autoimmune and metabolic studies of liver disease, alpha fetoprotein, HIV status, type and screen, other infectious serologies, and urine toxicology. Other investigations included cross-sectional imaging, pulmonary function tests, echocardiogram, and upper endoscopy and colonoscopy. Patients would undergo further assessments with specialists if necessary.

Several variables were collected in excel spreadsheets including patient and liver disease demographics, nutritional markers, laboratory investigations, and prognostic scores of liver disease. Patient demographics included age, sex, and history of alcohol use and smoking. Liver disease demographics comprised etiology of liver disease, diagnosis of hepatocellular carcinoma, and predominant pattern of liver injury. Nutritional markers included vitamin A, D, and E, zinc, albumin, pre-albumin, and body mass index (BMI). Laboratory investigations comprised bilirubin, INR, and creatinine. Prognostic scores of liver disease included the Child-Pugh-Turcott (CPT) score and sodium model for end-stage liver disease (MELD-Na). If patients had missing information, they were excluded from this study.

A deficient vitamin A level was £1.1 umol/L, a deficient vitamin D level was £74 nmol/L, a deficient vitamin E level was £17 umol/L, and a deficient zinc level was £640 ug/L. The data was analyzed to identify correlations between FSV and zinc deficiencies with nutritional markers and the severity of liver disease.

Statistical Analysis

Statistical analysis was performed with Fisher's exact test and multiple variable logistic regression analysis presented as odds ratio (OR) with 95% confidence intervals (CI). SAS 9.4 was used for statistical analysis and a p-value <0.05 was considered significant.

Results

There were 109 patients with cirrhosis assessed for LT at LHSC between January and June 2012. Patient and liver disease demographics can be seen in table 1. Laboratory investigations, nutritional markers, and FSV (A, D, and E) and zinc levels are presented in table 2. In patients with cirrhosis being assessed for LT, vitamin A deficiency occurred in 77%, vitamin D deficiency in 63%, vitamin E deficiency in 37%, and zinc deficiency in 84%. Of the patients included in this study, 17% were on a form of multivitamin or mineral supplement. The degree of correlation between FSV and zinc deficiency and prognostic scores for the severity of liver disease was assessed. Correlations between CPT scores and FSV and zinc deficiency can be seen in table 3 while correlations between MELD-Na range and FSV and zinc deficiency can be seen in table 4. Significant predictors of FSV and zinc deficiency were identified on multiple variable logistic regression analysis. These predictors can be seen in table 5.

Discussion

This study assessed the prevalence of FSV (A, D, and E) and zinc deficiency in patients with cirrhosis being assessed for LT at our institute. Vitamin and mineral deficiency is a marker of malnutrition. The degree of malnutrition in LT candidates is predictive of postoperative complications and outcomes. Therefore, malnutrition needs to be optimized in patients prior to LT to improve outcomes (20-22). Vitamin and mineral deficiencies were quite prevalent with zinc being the highest at 84% and vitamin E being the lowest at 37%.

Vitamin A deficiency ranged from 70-75% in prior studies, which was similar to the 77% deficiency rate present in this study (13,23). Other studies have shown vitamin D deficiency range between 66-92% in patients with cirrhosis, which is slightly higher than the vitamin D deficiency rate of 63% in our study (13,15,23-26). London, Ontario is in the northern hemisphere and we would expect higher levels of vitamin D deficiency especially with the winter months. This difference could possibly be attributed to a difference in methods of vitamin D measurement or due to increased supplementation by patients to compensate for the reduction in sunlight. Vitamin E prevalence was 37%, which is within the range of 3-44% seen in prior studies (13,23-27). Zinc deficiency was present in 84% of patients, which was higher then the range of zinc deficiency of 43-53% in

patients with cirrhosis in previous studies (28,29). This could be related to differences in the severity of liver disease between the studies.

Table 1. —**Patient and liver disease demographics of patients assessed for LT at LHSC.**

Demographic	Mean ± SD or Percentage (%)
Age (years)	54 ± 10
Sex	Male: 66%
	Female: 34%
BMI (kg/m^2)	27 ± 6
Smoker: Active	22%
Former	28%
Never	50%
Alcohol: Active	5%
Former	78%
Never	17%
Liver Disease: Hepatitis C	36%
Alcohol	20%
NASH	17%
Other	27%
HCC	15%
Liver enzyme elevation: Cholestatic	50%
Hepatic	35%
None	15%
Child Pugh score: A	29%
B	54%
C	17%
MELD-Na score	16 ± 5
Listed for transplant	44%
Transplanted	56%
Died	8%

SD = standard deviation, NASH = non-alcoholic steatohepatitis, HCC = hepatocellular carcinoma, MELD-Na = sodium model for end-stage liver disease

Table 2. — **Laboratory investigations and fat-soluble vitamin and zinc levels in patients being assessed for LT at LHSC.**

Parameter	**Mean ± SD**
Albumin (g/L)	33 ± 6
Total bilirubin (mmol/L)	48 ± 61
INR	1.4 ± 0.7
Creatinine (mmol/L)	76 ± 30
Prealbumin (g/L)	0.10 ± 0.07
Vitamin A (umol/L)	0.88 ± 0.86
Vitamin D (nmol/L)	69 ± 52
Vitamin E (umol/L)	24 ± 17
Zinc (ug/L)	477 ± 145

SD=standard deviation, INR=international normalized unit

Table 3. — **The correlation between the Child Pugh score and fat-soluble vitamins and zinc deficiency in patients being assessed for LT.**

Vitamin	Child Pugh A (%) (number)	Child Pugh B (%) (number)	Child Pugh C (%) (number)	P-Value
Vitamin A				
Normal (%)	56% (14)	40% (10)	4% (1)	0.0034
Deficient (%)	22% (18)	58% (49)	20% (17)	
Vitamin D				
Normal (%)	45% (18)	45% (18)	10% (4)	0.021
Deficient (%)	20% (14)	60% (41)	20% (14)	
Vitamin E				
Normal (%)	29% (20)	62% (43)	9% (6)	0.012
Deficient (%)	30% (12)	40% (16)	30% (12)	
Zinc				
Normal (%)	94% (15)	6% (1)	0% (0)	<0.001
Deficient (%)	15% (13)	67% (58)	18% (16)	

Table 4. — **The correlation between the MELD-Na range and fat-soluble vitamins and zinc deficiency in patients being assessed for LT.**

Vitamin	MELD-Na <10	MELD-Na 10-20	MELD-Na >20	P-Value
Vitamin A				
Normal (%)	24%	68%	8%	0.028
Deficient (%)	7%	70%	23%	
Vitamin D				
Normal (%)	18%	75%	7%	0.025
Deficient (%)	7%	67%	26%	
Vitamin E				
Normal (%)	13%	73%	14%	0.19
Deficient (%)	8%	64%	28%	
Zinc				
Normal (%)	53%	47%	0%	<0.001
Deficient (%)	3%	74%	23%	

MELD-Na = sodium model for end-stage liver disease

The etiology of liver disease did not correlate with fat-soluble vitamin (A,D, and E) and zinc deficiency in our study. This is consistent with prior studies of FSVs, which did not show a clear association with these deficiencies and etiology of cirrhosis (13,23). Patients with cholestatic liver disease are at an increased risk of FSV deficiency (30). While cholestasis did correlate with vitamin D deficiency, it did not correlate with the other vitamin and mineral deficiencies on multiple logistic regression analysis. We did not see a seasonal variation in vitamin D deficiency in our patients despite our colder climate. A seasonal variation in vitamin D deficiency has

Table 5. — **Significant predictors of fat-soluble vitamin and zinc deficiency on multivariable logistic regression**

Variable	OR	95% CI	P-Value
Vitamin A Deficiency			
Albumin	0.78	0.65-0.94	0.0069
Vitamin D Deficiency			
Cholestasis	3.53	1.40-8.89	0.0073
Albumin	0.83	0.73-0.94	0.0032
Vitamin E Deficiency			
Albumin	0.85	0.74-.097	0.015
Zinc Deficiency			
Age	0.83	0.72-0.96	0.012
Albumin	0.59	0.42-0.82	0.0036
MELD=Na	1.43	1.05-1.94	0.021

MELD-Na=sodium model for end-stage liver disease.

been shown in patients with cirrhosis in the past (31). We were not able to accurately assess sequelae of FSV and zinc deficiency in this study. Significant complications of vitamin A, E, and zinc deficiency were not clearly identified

While FSV and zinc deficiency did not correlate with nutritional markers, such as, pre-albumin and body mass index, all deficiencies did correlate with a low albumin on multiple logistic regression analysis. This has been shown in a prior study (23). While free fatty acids are bound to albumin when travelling in serum, FSV travel through serum in lipoproteins to the liver (32). On the other hand, zinc is mainly bound to albumin for serum transport (33). The binding of albumin to zinc in serum would explain why a low albumin would lead to a low zinc level. However, this would not explain why FSV are low in patients with low albumin. This may likely be due to the fact that as albumin is a synthetic marker of liver dysfunction, a low albumin would correlate with a lack of protein synthesis. Thus, lipoproteins in the liver would be reduced leading to a low level of FSVs in patients with cirrhosis.

While only zinc deficiency correlated with MELD-Na on multiple logistic regression analysis, MELD-Na was close to reaching statistical significance for the FSVs. As the liver is the main organ involved in zinc metabolism, a higher MELD-Na would be an indication of more severe liver disease and thus, a lower zinc level due to reduced metabolism. This has been correlated in prior studies (34). When we stratified MELD-Na into three groups of severity and CPT scores, most FSV and zinc deficiencies correlated with severe liver disease. Several studies have looked at FSV deficiencies in the past and shown a correlation with the severity of liver disease (23-26). Improving the nutritional status of patients with cirrhosis leads to better outcomes and makes identifying the features of malnutrition absolutely necessary (35). Improvement in vitamin A deficiency with supplementation in patients with cirrhosis led to an improvement in dark adaptation (36). Patients awaiting LT with osteopenia or osteoporosis treated with vitamin D, calcium, and a bisphosphonate had an improvement in bone mineral density (37). Correction of zinc deficiency in patients with cirrhosis and hepatic encephalopathy may be beneficial (18).

There are several limitations in this study. This is a single center experience. We did not correlate serum levels of FSV and zinc with liver stores. Serum levels may not completely correlate with liver stores for some vitamins or nutrients (38). A proportion of our patients were on multivitamin and nutrient supplements for which we did not know the exact composition. This may confound the results obtained in this study. We did not utilize more accurate measures of malnutrition, such as, the subjective global assessment or sarcopenia scores. Dietary intake of various vitamins and nutrients was not measured which could alter the results in this patient population. In addition we did not factor out the water weight component due to ascites into the weight calculation when determining BMI. This may further confound the results. However, our study was still capable of identifying some important associations in patients with cirrhosis with FSV and zinc deficiency.

In conclusion, FSV and zinc deficiency is quite prevalent in patients with cirrhosis. A low albumin was the only clinical predictor that correlated with all FSV and zinc deficiencies while other clinical predictors varied depending on the deficiency. Cholestasis correlated with vitamin D deficiency and high MELD = Na and age correlated with zinc deficiency. Hepatologists and gastroenterologists should routinely assess for FSV and zinc levels when assessing patients with cirrhosis. Further randomized controlled trials are necessary to confirm improvement in clinical outcomes when supplementing patients with these deficiencies.

References

1. CARVALHO L., PARISE E.R. Evaluation of nutritional status of nonhospitalized patients with liver cirrhosis. *Arq. Gastroenterol*., 2006., **43** : 269-74.
2. MERLI M., GIUSTO M., GENTILI F. *et al*. Nutritional status : its influence on the outcome of patients undergoing liver transplantation. *Liver Int*., 2010, **30** : 208-214.
3. QIN H., LI H., XING M., *et al*. Nutritional support treatment for severe chronic hepatitis and posthepatitic cirrhosis. J Huazhong Univ Sci *Technolog. Med. Sci*., 2006. **26** : 217-220.
4. KALAITZAKIS E., SIMRÉN M., OLSSON R. *et al*. Gastrointestinal symptoms in patients with liver cirrhosis : associations with nutritional status and health-related quality of life. *Scand. J. Gastroenterol*., 2006, **41** : 1464-72.
5. GUNSAR F., RIAMONDO ML., JONES S *et al*. Nutritional status and prognosis in cirrhotic patients. *Aliment. Pharmacol*. Ther. 2006., **24** : 563-72.
6. ALBERINO F., GATTA A., AMODIO P *et al*. Nutrition and survival in patients with liver cirrhosis. *Nutrition*, 2001, **17** : 445-50.
7. PLAUTH M., CABRE E., RIGGIO O., ASSIS-CAMILO M., PIRLICH M., KONDRUP J. ESPEN. Guidelines on enteral nutrition : liver disease. *Clin. Nutr*. 2006, **25** : 285-94.
8. MONTANO-LOZA A.J., MEZA-JUNCO J., PRADO C.M., LIEFFERS JR., BARACOS V.E., BAIN V.G., SAWYER M.B. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2012., **10** :166-73.

9. HANAI T., SHIRAKI M., NISHIMURA K., OHNISHI S., IMAI K., SUETSUGU A., TAKAI K., SHIMIZU M., MORIWAKI H. Sarcopenia impairs prognosis of patients with liver cirrhosis. *Nutrition*., 2015, **31** : 193-9.
10. PURNAK T., YILMAZ Y. Liver disease and malnutrition. *Best Pract Res Clin Gastroenterol*. 2013, **27** : 619-29.
11. CHEUNG K., LEE S.S., RAMAN M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease., and nutrition management strategies. *Clin Gastroenterol*. *Hepatol*., 2012, **10** : 117-125
12. TSIAOUSI ET., HATZITOLIOS A.I., TRYGONIS S.K., SAVOPOULOS CG. Malnutrition in end stage liver disease : Recommendations and nutritional support. *J. Gastroenterol*. *Hepatol*., 2008, **23** : 527-533
13. VENU M., MARTIN E., SAEIAN K., GAWRIEH S. High prevalence of vitamin A deficiency and vitamin D deficiency in patients evaluated for liver transplantation. *Liver Transpl.* ,2013, **19** : 627-633
14. PERES W.A., CHAVES G.V., GONCALVES J.C.S., RAMALHO A., COELHO H.S.M. Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. *Br. J. Nutr.,* 2011, **106** : 1724-1731
15. ARTEH J., NARRA S., NAIR S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig*. *Dis*. *Sci*., 2010., **55** : 2624-2628
16. HAN Y.P., KONG M., ZHENG S., REN Y., ZHU L., SHI H., DUAN Z. Vitamin D in liver diseases : from mechanism to clinical trials. *J. Gastroenterol*. *Hepatol*., 2013., **28** (suppl. 1) : 49-55
17. LOOK M.P., REICHEL C., VON FALKENHAUSEN M., HAHN C., STOCKINGER K., VON BERGMANN K., RAO G.S., SPENGLER U., SAUERBRUCH T. Vitamin E status in patients with liver cirrhosis : normal or deficient? *Metabolism* 1999., **48** : 86-91
18. STAMOULIS I., KOURAKLIS G., THEOCHARIS S. Zinc and the liver : an active interaction. *Dig*. *Dis*. *Sci*., 2007, 52 : 1595-1612
19. MOHOMMAD M.K., ZHOU Z., CAVE M., BARVE A., MCCLAIN C.J. Zinc and liver disease. *Nutr. Clin*. *Pract*., 2012, **27** : 8-20
20. PIKUL J., SHARPE M.D., LOWNDES R., GHENT C.N. Degree of preoperative malnutrition is predictive of postoperative morbidity and mortality in liver transplant recipients. *Transplantation,* 1994, **57** : 469-72.
21. HARRISON J., MCKIERNAN J., NEUBERGER J.M. A prospective study on the effect of recipient nutritional status on outcome in liver transplantation. *Transpl*. *Int*., 1997, **10** : 369-74.
22. MERLI M., GIUSTO M., GENTILI F., NOVELLI G., FERRETTI G., RIGGIO O., CORRADINI S.G., SICILIANO M., FARCOMENI A., ATTILI AF., BERLOCO P., ROSSI M. Nutritional status : its influence on the outcome of patients undergoing liver transplantation. *Liver. Int*., 2010, **30** : 208-14.
23. ABBOTT-JOHNSON W., KERLIN P., CLAGUE A., JOHNSON H., CUNEO R. Relationships between blood levels of fat soluble vitamins and disease etiology and severity in adults awaiting liver transplantation. *J Gastroenterol*. *Hepatol*., 2011, **26** : 1402-10.
24. STOKES C.S., KRAWCZYK M., REICHEL C., LAMMERT F., GRÜNHAGE F. VITAMIN D deficiency is associated with mortality in patients with advanced liver cirrhosis. *Eur. J. Clin*. *Invest*. 2014., **44** : 176-83.
25. MALHAM M., JØRGENSEN S.P., OTT P., AGNHOLT J., VILSTRUP H., BORRE M., DAHLERUP J.F. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. *World J. Gastroenterol*., 2011, **17** : 922-5.
26. FISHER L., FISHER A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin*. *Gastroenterol*. *Hepatol*., 2007, **5** : 513-20.
27. ARRIA A.M., TARTER R.E., WARTY V., VAN THIEL D.H. Vitamin E deficiency and psychomotor dysfunction in adults with primary biliary cirrhosis. *Am. J. Clin*. *Nutr.,* 1990, **52** : 383-90.
28. SCHNEIDER A.C., PINTO R.B., FRÖEHLICH P.E., HAMMES T.O., SILVEIRA T.R. Low plasma zinc concentrations in pediatric patients with cirrhosis. *J. Pediatr. (Rio J),* 2009, **85** : 359-64.
29. POO J.L., ROSAS-ROMERO R., RODRÍGUEZ F., SILENCIO J.L., MUÑOZ R., BOURGES H., URIBE M. Serum zinc concentrations in two cohorts of 153 healthy subjects and 100 cirrhotic patients from Mexico City. *Dig*. *Dis*., **13** : 136-42.
30. GOSSARD A.A. Care of the cholestatic patient. *Clin*. *Liver. Dis*., 2013, **17** : 331-44.
31. GUZMÁN-FULGENCIO M., GARCÍA-ÁLVAREZ M., BERENGUER J., JIMÉNEZ-SOUSA M.Á., COSÍN J., PINEDA-TENOR D., CARRERO A., ALDÁMIZ T., ALVAREZ E., LÓPEZ JC., RESINO S. Vitamin D deficiency is associated with severity of liver disease in HIV/HCV coinfected patients. *J. Infect*., 2014, **68** : 176-84.
32. IQBAL J., HUSSAIN M.M. Intestinal lipid absorption. *Am. J. Physiol*. *Endocrinol*. *Metab*., 2009, **296** : E1183-94.
33. KIILERICH S., CHRISTIANSEN C. Distribution of serum zinc between albumin and alpha 2-macroglobulin in patients with different zinc metabolic disorders. *Clin*. *Chim*. *Acta*., 1986, **154** : 1-6.
34. KAZUNARI I., HIRAYUKI E., SHUHEI N., NOBUHIRO A., YOSHIYUKI S., YOSHINORI I., HIRONORI T., NAOTO I., TOMOYUKI T., MASAKI S., HIROYASU I., HIROKO I., YASUHIRO T., KAZUHIDE H. Serum zinc value in patients with hepatitis virus-related chronic liver disease : association with the histological degree of liver fibrosis and with the severity of varices in compensated cirrhosis. *J. Clin*. *Biochem*. *Nutr.,* 2014, **55** : 147-52.
35. CAMPILLO B., RICHARDET J.P., BORIES P.N. Enteral nutrition in severely malnourished and anorectic cirrhotic patients in clinical practice. *Gastroenterol*. *Clin*. *Biol*., 2005, **29** : 645-51.
36. ABBOTT-JOHNSON W.J., KERLIN P., ABIAD G., CLAGUE A.E., CUNEO R.C. Dark adaptation in vitamin A-deficient adults awaiting liver transplantation : improvement with intramuscular vitamin A treatment. *Br. J. Ophthalmol*., 2011, **95** : 544-8.
37. KAEMMERER D., BENJAMIN S., GABRIELE L., GUNTER W., UTZ S., MERTEN H. Treatment of bone loss in patients with chronic liver disease awaiting liver transplantation. *Transplant Res*., 2012, **1** : 7.
38. UKLEJA A., SCOLAPIO JS., MCCONNELL J.P., SPIVEY J.R., DICKSON R.C., NGUYEN J.H., O'BRIEN P.C. Nutritional assessment of serum and hepatic vitamin A levels in patients with cirrhosis. *JPEN J. Parenter. Enteral*. *Nutr*., 2002, **26** : 184-8.
39. KIILERICH S., CHRISTIANSEN C. Distribution of serum zinc between albumin and alpha 2-macroglobulin in patients with different zinc metabolic disorders. *Clin*. *Chim*. *Acta,* 1986, **154** : 1-6.
40. KAZUNARI I., HIRAYUKI E., SHUHEI N., NOBUHIRO A., YOSHIYUKI S., YOSHINORI I., HIRONORI T., NAOTO I., TOMOYUKI T., MASAKI S., HIROYASU I., HIROKO I., YASUHIRO T., KAZUHIDE H. Serum zinc value in patients with hepatitis virus-related chronic liver disease : association with the histological degree of liver fibrosis and with the severity of varices in compensated cirrhosis. *J. Clin*. *Biochem*. *Nutr.,* 2014, **55** : 147-52.
41. CAMPILLO B., RICHARDET JP., BORIES PN. Enteral nutrition in severely malnourished and anorectic cirrhotic patients in clinical practice. *Gastroenterol*. *Clin*. *Biol*., 2005, **29** : 645-51.
42. ABBOTT-JOHNSON W.J., KERLIN P., ABIAD G., CLAGUE AE., CUNEO R.C. Dark adaptation in vitamin A-deficient adults awaiting liver transplantation : improvement with intramuscular vitamin A treatment. *Br. J. Ophthalmol*., 2011, **95** : 544-8.
43. KAEMMERER D., BENJAMIN S., GABRIELE L., GUNTER W., UTZ S., MERTEN H. Treatment of bone loss in patients with chronic liver disease awaiting liver transplantation. *Transplant*. *Res*., 2012, **1** : 7.
44. UKLEJA A., SCOLAPIO JS., MCCONNELL J.P., SPIVEY JR., DICKSON RC., NGUYEN J.H., O'Brien PC. Nutritional assessment of serum and hepatic vitamin A levels in patients with cirrhosis. *JPEN J. Parenter. Enteral*. *Nutr.,* 2002, **26** : 184-8.