Original Research Article

Outcome Prediction for Patients with Cirrhosis of the Liver in a Tertiary Care Centre: Relation to Serum Vitamin C

Debkumar Ray[1], Bholanath Maji[2]

[1]Associate Professor, [2]Assistant Professor,
Biochemistry Department, Burdwan Medical College and Hospital, Burdwan, West Bengal

Corresponding Author: Bholanath Maji

ABSTRACT

There have been many studies concerning the prognostic factors in cirrhosis of liver, but without any unanimous conclusion. Nutritional factors have been shown to affect the prognosis of cirrhosis. With this background, the authors tried to assess the prognostic importance of vitamin C, if any, in cirrhosis of liver. The present study was conducted in the Department of Biochemistry of a tertiary care medical college and hospital. Serum vitamin C and INR of 91 LC patients with esophageal varices and ascites (group 1), and 78 LC patients without esophageal varices and ascites (group 2) were estimated. Vitamin C was significantly decreased and INR was highly significantly increased in group 1 with respect to group 2. Depletion of vitamin C levels in serum may be related to the progress of cirrhosis of liver, but this needs to be validated by further studies in larger number of subjects. Vitamin C may be considered as a useful biomarker of antioxidant status in cirrhosis of liver for elaboration of monitoring.

Keywords: cirrhosis of liver, vitamin C, INR, prognosis

INTRODUCTION

Cirrhosis is the end-stage condition of many types of chronic liver diseases. [1] Chronic hepatitis B is the primary cause of liver cirrhosis (LC) in the Asia-Pacific region. [2] LC is a major yet largely preventable and underappreciated cause of global health loss. Variations in cirrhosis mortality at the country level reflect differences in prevalence of risk factors such as hepatitis B and C infection and alcohol use. [3] Although the causes of LC are multifactorial, there are some pathological characteristics that are common to all cases of LC, including degeneration and necrosis of hepatocytes, and replacement of liver parenchyma by fibrotic tissues and regenerative nodules, and loss of liver function. [4]

The economic and social burden of LC is immense considering decreased quality of life, the disability of labor, poorer physical activity, and need for frequent hospitalizations in patients with LC. Although liver biopsy remains the reference standard for evaluating the extent of liver fibrosis in patients with chronic liver diseases, several noninvasive methods such as acoustic radiation force impulse (ARFI) and transient elastography (TE) have been developed as alternatives to liver biopsies. [5] There are numerous studies concerning the natural history and prognostic factors in cirrhosis. [6] These include a variety of parameters, but are not without their drawbacks; so, while these are often conventionally used to determine the functional ability of the liver and condition of the patient, they are not accepted universally. To assess the prognosis in cirrhosis, several methods have been advocated, such as Child-Pugh score, Model for End-Stage Liver Disease score, etc. [7]

Tajika et al stated that evaluation of energy metabolism can be used to predict survival in patients with viral LC. [8] Hanai et al found that sarcopenia, characterized by the loss of skeletal muscle mass, impairs prognosis of patients with LC. [9] Thus, nutritional factors have been shown to affect the prognosis of cirrhosis. With this background, the authors tried to assess the prognostic importance of vitamin C, if any, in LC.

MATERIALS AND METHODS

This study was a hospital-based study conducted in the Department of Biochemistry of a tertiary care medical college and hospital of West Bengal. The study was approved by the local ethical committee and all patients gave their informed consent to take part in this investigation.

The duration of the present study was 11 months and included 91 LC patients with esophageal varices and ascites (group 1) attending the outpatient department (OPD). In addition, 78 LC patients without esophageal varices and ascites (group 2), who were age and sex matched with group 1, were also included. Complete history and physical examination of all patients were undertaken. Exclusion criteria included alcoholics, smokers, abnormal dietary habits, cholestasis, malabsorption syndromes and subjects who had received any vitamin C supplements within the last month.

Venous blood sample was collected from each patient after 12 hours of fasting. All samples were coded and assayed in a blind fashion by an investigator who was unaware of the subjects' clinical status.

Serum vitamin C was assayed by 2,3-dinitrophenylhydrazine method. [10] Prothrombin time (INR) was assayed in patients as a prognostic measure of liver function, because INR remains a practically useful and statistically significant correlate of mortality risk in patients with end-stage liver disease; [11] it is also widely available and is likely continue to be used as an indicator of survival in patients with end-stage liver disease. [12]

Statistical analysis of the data was performed by using Statistical Package for Social Sciences (SPSS version 16) and inferences were drawn. $p < 0.05$ was considered to be significant and $p < 0.001$ highly significant.

RESULTS

Table 1. Serum vitamin C levels (in micromole/L) and INR in patients

	Vitamin C	INR
Group 1	39+4.6	2.1+0.19
Group 2	41+5.4	1.3+0.12

t test results
For vitamin C:
p value and statistical significance:
 The two-tailed p value equals 0.0102
 By conventional criteria, this difference is considered to be statistically significant.
Confidence interval:
 The mean of group 1 minus group 2 equals -2.000
 95% confidence interval of this difference: From -3.519 to -0.481
Intermediate values used in calculations:
 t = 2.6002
 df = 167
 standard error of difference = 0.769
SEM for groups 1 and 2 are respectively 0.482 and 0.611

For INR:
p value and statistical significance:
 The two-tailed p value is less than 0.0001
 By conventional criteria, this difference is considered to be extremely statistically significant.
Confidence interval:
 The mean of group 1 minus group 2 equals 0.8000
 95% confidence interval of this difference: From 0.7508 to 0.8492
Intermediate values used in calculations:
 t = 32.0951
 df = 167
 standard error of difference = 0.025
SEM for groups 1 and 2 are respectively 0.0199 and 0.0136

DISCUSSION

The hepatotoxicity of several free radical-generating compounds has been found. The involvement of free radical reactions in the pathogenesis of liver injury has been investigated for many years in a few defined experimental systems using ethanol as prooxidant agent. [13] Amalia et al concluded that quercetin has beneficial effects on liver fibrosis in rats by enhancing antioxidant enzyme activity and decreasing the pro-oxidant effect; thus quercetin decreased the effects of free radicals and delayed progression of pathogenesis in cirrhosis. [14] Barja et al showed that a diet supplying an amount of vitamin C 40 times higher than the minimum daily requirement to avoid scurvy increases the global antioxidant capacity and is of protective value against endogenous lipid and protein oxidation in the liver under normal nonstressful conditions. [15] Vitamin C readily scavenges reactive oxygen and nitrogen species, such as superoxide and hydroperoxyl radicals, aqueous peroxyl radicals, singlet oxygen, ozone, peroxynitrite, nitrogen dioxide, nitroxide radicals, and hypochlorous acid, [16] thereby effectively protecting other substrates from oxidative damage. Vitamin C can also act as a coantioxidant by regenerating the antioxidant α-tocopherol (vitamin E) from the α-tocopheroxyl radical, produced via scavenging of lipid-soluble radicals. This is also another potentially important function because in vitro experiments have shown that α-tocopherol can act as a prooxidant in the absence of coantioxidants such as vitamin C. [17] Vitamin C has also been shown to regenerate urate, glutathione, and β-carotene in vitro from their respective one-electron oxidation products, ie, urate radicals, glutathiyl radicals, and β-carotene radical cations. [18] As because vitamin C is an antioxidant, it is gradually depleted by increasing concentrations of free radicals as cirrhosis progresses; this might be the reason of significantly decreased levels of vitamin C in group 1 with respect to group 2 in our study (table 1).

The liver is a very important site of almost all metabolic pathways in our body and vitamin C takes part in many of these biochemical reactions. Carnitine is essential for the transport of activated long-chain fatty acids into the mitochondria, and then only fatty acids undergo breakdown via beta oxidation. Vitamin C is required as a cofactor for mono and dioxygenases involved in the biosynthesis of carnitine, and also peptide amidation and tyrosine metabolism. Vitamin C is also involved in the metabolism of cholesterol to bile acids via the enzyme cholesterol 7α-monooxygenase and in steroid metabolism in the adrenals. Hydroxylation of aromatic drugs and carcinogens by hepatic cytochrome P450 is also enhanced by reducing agents such as vitamin C. [19] All these reactions are hampered when vitamin C levels are decreased, and lead to impairment of hepatic function, which is evident by the increasing value of INR with progress of disease, in our study (table 1).

This study has limitations that must be considered. To assess vitamin C, 2,3-dinitrophenylhydrazine method was used. Vitamin C can be estimated by various methods, but the present method was employed as it is the most commonly used and time tested method. Also, number of patients in the study groups was not large. Thus, care must be taken in extrapolating the present findings to other populations. Patients were taking a number of medications to control symptoms. However, these treatments are characteristic of patients with LC and do not affect serum vitamin C levels. Despite these limitations, we believe that our study points towards using it as an important, promising prognostic marker for LC. As our findings point to a decrease in the antioxidant vitamin C, the problem of oxidative stress in LC should also be further investigated in a larger number of patients, and other antioxidants and markers of oxidative stress should be assessed.

CONCLUSION

The results of our study suggest that depletion of vitamin C levels in serum may be related to the progress of LC, but this needs to be validated by further studies in larger number of subjects. Vitamin C may be considered as a useful biomarker of antioxidant status in LC for elaboration of monitoring and also for planning of treatment strategy.

REFERENCES

1. Zhou W-C, Zhang Q-B, Qiao L. Pathogenesis of liver cirrhosis. World J Gastroenterol. 2014; 20(23): 7312–24.
2. Lv GC, Yao JM, Yang YD, Zheng L, Sheng JF, Chen Y, Li LJ. Efficacy of combined therapy in patients with hepatitis B virus-related decompensated cirrhosis. World J Gastroenterol. 2013;19:3481–3486.
3. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 2014;12:145.
4. Ferrell L. Liver pathology: cirrhosis, hepatitis, and primary liver tumors. Update and diagnostic problems. Mod Pathol. 2000; 13:679–704.
5. Nishikawa H, Osaki Y. Liver Cirrhosis: Evaluation, Nutritional Status, and Prognosis. Mediators Inflamm. 2015;2015:872152.
6. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V,et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999; 30(5):890-5.
7. Vitale A, Volk ML, De Feo TM, et al. A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list. JR Hepatol. 2014; 60(2):290-7.
8. Tajika M, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, Moriwaki H. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition. 2002;18(3):229-34.
9. Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition. 2015;31(1):193-9.
10. Lowry OH, Lopez JA, Bessey OA. The determination of ascorbic acid in small amounts of blood serum. J Biol Chem.1945; 160:609–15
11. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology. 2011;140:1952–60
12. Kamath PS, Kim WR. The model for end-stage liver disease (MELD) Hepatology. 2007;45:797–805.
13. Poli G Liver damage due to free radicals. *BMB*. 1993;49(3):604-20
14. Quercetin Prevents Oxidative Stress in Cirrhotic Rats. Amália PM, Possa MN, Augusto MC, Francisca LS. Dig Dis Sci. 2007;52:2616-21
15. Barja G, López-Torres M, Pérez-Campo R, Rojas C, Cadenas S, Prat J, et al. Dietary vitamin C decreases endogenous protein oxidative damage, malondialdehyde, and lipid peroxidation and maintains fatty acid unsaturation in the guinea pig liver.Free Radic Biol Med. 1994;17(2):105-15.
16. Halliwell B. Vitamin C: antioxidant or pro-oxidant in vivo? Free Radic Res. 1996; 25(5):439-54.
17. Bowry VW, Mohr D, Cleary J, Stocker R. Prevention of tocopherol-mediated peroxidation in ubiquinol-10-free human low density lipoprotein. J Biol Chem. 1995; 270(11):5756-63.
18. Edge R, Truscott TG. Prooxidant and antioxidant reaction mechanisms of carotene and radical interactions with vitamins E and C. Nutrition. 1997;13(11-12):992-4.
19. Burri BJ, Jacob RA.Human metabolism and the requirement for vitamin C. In: Packer L, Fuchs J, eds. Vitamin C in health and disease. New York: Marcel Dekker Inc, 1997:341–66.

******