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Decreased Hepatic Selenium Content in Alcoholic Cirrhosis

BRAD M. DWORKIN, MD, WILLIAM S. ROSENTHAL, MD, ROSALYN E. STAHL, MD, and NARENDRA K. PANESAR, MD

Selenium deficiency has been implicated as contributing to hepatic injury in alcoholics. The mechanism by which this occurs is most likely lipoperoxidation secondary to decreased activity of the selenoenzyme glutathione peroxidase. To further assess this relationship, we measured selenium content in autopsy livers in 12 patients with alcoholic cirrhosis compared to 13 patients matched for age and sex dying from other causes, mostly with cardiopulmonary diseases. The mean (± SEM) hepatic selenium content in cirrhosis was 0.731 ± 0.077 μg/g dry weight versus 1.309 ± 0.166 μg/g in controls ($P < 0.005$; Student's t test). Clinical and biochemical indices of significant hepatic dysfunction, including encephalopathy, ascites, and elevations of serum bilirubin or prothrombin time, were only present in the cirrhotic group. A significant inverse correlation between hepatic selenium content and the prothrombin time was noted ($r = -0.50$; $P < 0.02$). No significant relationships between hepatic selenium and the abnormalities of bilirubin, albumin, or aspartate aminotransferase were found. We conclude that significantly decreased hepatic selenium stores are present in patients with severe alcoholic cirrhosis compared to controls. The magnitude of that selenium deficit does correlate with some indices of hepatic function, specifically the prothrombin time. These data lend further support to a true selenium deficiency state in alcoholic cirrhosis. It is highly possible that selenium deficiency represents an important link, synergistically joining the nutritional and hepatotoxic backgrounds of alcoholic liver injury and cirrhosis.

KEY WORDS: selenium; alcoholism; cirrhosis.

Selenium deficiency has been demonstrated experimentally to cause hepatic injury (1). This probably is a result of accentuated lipoperoxidation due to decreased activity of the selenoenzyme glutathione peroxidase (2–5). We and others have previously shown markedly diminished amounts of plasma and erythrocyte selenium in alcoholics without liver disease, and more dramatic decreases in those with severe liver disease (2, 3, 6–9). In alcoholics the magnitude of the selenium abnormality correlated with parameters of liver function (2, 3, 9). From this it appears that selenium deficiency is not simply a result of liver disease, but may contribute directly to hepatocellular injury (2, 3, 8). Selenium may represent an important link between the toxic effects of alcohol and a specific nutritional deficiency that combines to result in enhanced hepatic toxicity. However, selenium is transported in the blood

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From the Sarah C. Upham Division of Gastroenterology, the Department of Medicine and the Department of Pathology, New York Medical College, Valhalla, New York.

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Address for reprint requests: Dr. Brad Dworkin, M.D., New York Medical College, Munger Pavilion, Room 206, Valhalla, NY 10595.

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bound to a specific plasma protein, probably synthesized in the liver (10, 11). Therefore, plasma or erythrocyte selenium determinations could be influenced by diminished hepatic protein synthesis, frequently found in cirrhosis (12).

Likewise, alterations in plasma volume commonly seen in advanced liver disease could effect these blood levels. Finally short-term dietary intakes of selenium could have a profound effect on plasma or serum selenium levels (13). It is unclear whether these established abnormalities of blood values reflect hepatic selenium stores. A previous report demonstrated decreased hepatic selenium content in Scandinavians with cirrhosis versus normals (14). However, the cirrhotics were older than the controls, and, as selenium levels may decline with age, this difference could have affected the results (14, 15). Scandinavians are also endemically low in selenium due to poor dietary intake secondary to low soil selenium content (16). No other clinical, biochemical, or histologic data were reported in that series (14). In addition, many of the hepatic selenium values both in normals and cirrhotics fell below the detection limit of the assay, making an accurate interpretation of mean values tenuous. In the present work, to further ascertain whether hepatic selenium deficiency exists in the presence of advanced alcoholic liver disease, we compared clinical and biochemical parameters and hepatic selenium content in patients with alcoholic cirrhosis to age- and sex-matched patients without significant hepatic disease.

MATERIALS AND METHODS

Autopsy liver samples were obtained from 25 patients at Westchester County Medical Center over a three-year period. Subjects were specifically chosen for inclusion in this study based in part upon the presence or absence of significant liver disease. In screening for control patients, any person with a prior history of liver disease or histologic evidence of significant liver disease was excluded.

The stored liver samples were first deparaffinized with xylene, and then lyophylized to stable dry weight. Hepatic selenium contact was determined by a previously described spectrofluorometric method (2, 6, 17, 18). All charts were reviewed for clinical and biochemical data. That data reported represent the last available data prior to the patient's death. All hepatic pathology was reviewed by a pathologist (R.E.S.) blinded with respect to the patient's clinical data.

Statistical determinations were performed including the Student's t test for nonpaired data, chi square, and correlation coefficients (Pearson r), where appropriate (19). All values are expressed a mean ± SEM.

The study was approved by the New York Medical College Committee for the Protection of Human Subjects.

RESULTS

Demographic data concerning the two groups are given in Table 1. Note that 11 cirrhotic patients gave a history of alcohol abuse, whereas hepatic histology and the clinical setting were clearly suggestive of alcoholic cirrhosis in all cases. Age and sex were similar between the groups. No patient was positive for hepatitis B surface antigen. No patient had a history of intravenous drug use.

Pathologically, the noncirrhotic group did have some hepatic abnormalities. Although mild fatty changes and sinusoidal dilatation are not uncom-

TABLE 1. PATIENT DATA

Parameter	*Cirrhotic* (N = *12*)	*Noncirrhotic* (N = *13*)
Age	57.3 ± 3.7	62.6 ± 4.1
	P = NS	
Sex		
Male	8	7
Female	4	6
Principal cause of death	Cirrhosis (N = 11) Myocardial infarction (N = 1)	Myocardial infarction (N = 5) Respiratory failure (N = 4) Pneumonia/sepsis (N = 3) Oral cancer (N = 1)
History of alcohol abuse	11/12 (92%)	3/13 (23%)
	$P < 0.002$ (chi square)	
Hepatic histology	Micronodular cirrhosis (N = 12)	Centrilobular congestion and necrosis (N = 9) Mild fatty changes (N = 2) Sinusoidal congestion (N = 2)

TABLE 2. LIVER FUNCTION IN CIRRHOTIC AND NONCIRRHOTIC GROUPS

Parameter	*Cirrhotic*	*Noncirrhotic*	*Significance (P)*
Bilirubin (g/dl)	10.2 ± 2.2 (N = 12)	0.9 ± 0.2 (N = 12)	0.004*
Prothrombin time (PT) (% of control)	1.85 ± 0.19 (N = 11)	1.08 ± 0.03 (N = 9)	0.001*
PT (sec)	21.3 ± 2.1 (N = 11)	13.4 ± 0.6 (N = 11)	0.002*
Aspartate aminotransferase (AST) (units/liter)	133.7 ± 43.6 (N = 11)	135.4 ± 61.5 (N = 12)	NS*
Albumin (g/dl)	2.7 ± 0.2 (N = 11)	3.1 ± 0.1 (N = 12)	NS*
Hepatic encephalopathy	3/12 (25%)	0/13 (0%)	<0.002†
Ascites	7/12 (58%)	0/13 (0%)	0.0001†
HB_sAg	0/12 (0%)	0/12 (0%)	NS†

*Student's t test.
†Chi square.

mon in the liver at autopsy, centrilobular congestion and occasional mild necrosis was present in nine cases. These findings are compatable with the clinical data of severe cardiopulmonary disease accounting for the death of nine noncirrhotic patients (Table 1), are felt to represent agonal liver changes, and probably account for the mild increase in AST in that group (Table 2).

The mean hepatic selenium content in 12 cirrhotic patients was 0.731 ± 0.077 μg/g dry weight versus 1.309 ± 0.166 μg/g in 13 noncirrhotic controls ($P <$ 0.005; Student's t test) (Figure 1). All relationships remain the same whether the three control patients with a history of alcohol ingestion are excluded or included.

Clinical and biochemical indices of hepatic dysfunction, including the presence of hepatic encephalopathy and ascites, and elevations in serum bilirubin and prothrombin time were significantly more prevalent in the cirrhotic group. (Table 2). Correlation coefficients were derived for hepatic selenium content compared to liver function parameters for both groups combined (Table 3). A significant inverse correlation between hepatic selenium and the prothrombin time was noted ($r = -0.50$; $P < 0.02$) (Figure 2), but only a weaker relationship between hepatic selenium and bilirubin was present ($r = -0.28$; $P = 0.1$). It is noteworthy that no significant relationships between hepatic selenium and the abnormalities in AST or serum albumin were found. When the cirrhotic group was considered separately, correlations between hepatic selenium and PT ($r = -0.49$), bilirubin ($r = 0.38$), AST ($r = 0.2$) and albumin ($r = 0.41$) were present, but, perhaps due to sample size, failed to reach statistical significance.

DISCUSSION

Deficiency of the essential trace element selenium has significant implications in the pathogenesis of liver disease and cirrhosis, particularly for the

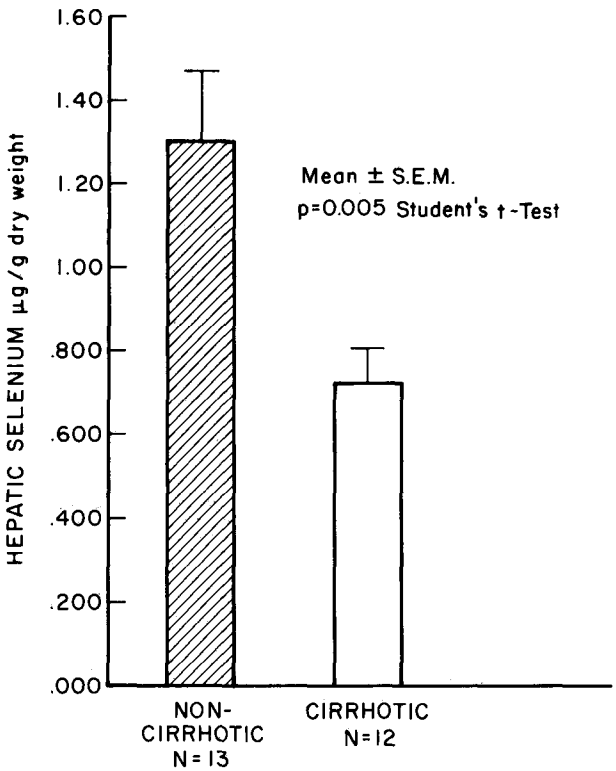

Fig 1. Hepatic selenium content in patients with alcoholic cirrhosis and noncirrhotic controls.

TABLE 3. HEPATIC SELENIUM CONTENT VS LIVER FUNCTION TESTS IN CIRRHOTICS AND CONTROLS*

Parameter	*Correlation Coefficient* (r)	*Significance* (P)
Bilirubin	−0.28	0.1
Prothrombin time	−0.50	0.02
Aspartate aminotransferase	0.08	0.7
Albumin	0.2	0.4

*Both groups combined.

alcoholic. Enhanced hepatic lipoperoxidation has been postulated as an important contributor to alcoholic liver injury (12, 20). Decreased hepatic glutathione stores have been shown in alcoholics and are thought to contribute to lipoperoxidation (20). The selenoenzyme glutathione peroxidase utilizes glutathione as substrate and is a major pathway in the detoxification of lipid peroxides and other organic peroxides generated during cellular metabolism (4, 5, 21). This problem is accentuated by the finding that selenium deficiency experimentally affects hepatocyte glutathione metabolism, resulting in enhanced glutathione synthesis and release (22). It is probable that the alcoholic cannot respond to selenium deficiency with this compensatory increase in hepatic glutathione synthesis. Therefore, decreased availability of both glutathione and selenium are likely to act synergistically to promote lipoperoxidation and hepatic injury.

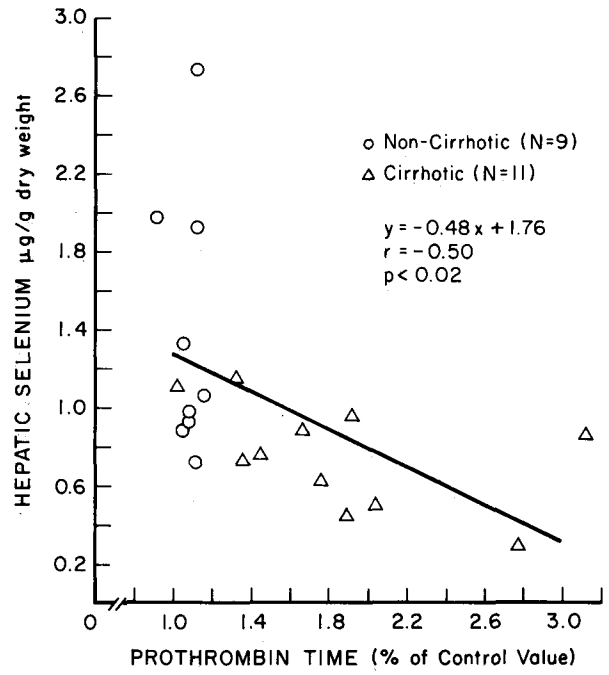

Fig. 2. Hepatic selenium content versus prothrombin time in patients with alcoholic cirrhosis and noncirrhotic controls.

We and others have previously shown abnormalities of serum, plasma, and erythrocyte selenium levels in alcoholics with and without liver disease (2, 3, 6–9). However, a myriad of nutritional or pathological factors present in alcoholic liver disease could influence those levels (23). The present study demonstrates that hepatic selenium stores are significantly reduced in autopsy livers in patients with cirrhosis compared to patients dying of other causes (Figure 1). Since the "control" group also had severe illnesses, not infrequently with some pathologic hepatic abnormalities, low serum albumin levels, and also had a high prevalence of cardiac disease, which epidemiologically may be associated with lower blood selenium levels, it is possible that this study underestimates the relative magnitude of the hepatic selenium deficiency in cirrhosis (24, 25). Although the methodology and geography varied, a comparison to another normal value for hepatic selenium (1.73 ± 0.24 µg/g) supports this contention (26).

As previously shown for blood values, hepatic selenium content did correlate with some measures of hepatic function (2). This is particularly true for the prothrombin time (Figure 2), and to a lesser extent, the bilirubin (Table 3). Selenium stores did not correlate with serum albumin levels, but this could reflect the severe illnesses in the controls, who had abnormally low albumin levels (Table 2). Interestingly, the height of the bilirubin and the prolongation in prothrombin time, but not the AST, have been shown to correlate with survival in alcoholic hepatitis (27–29). The relationships between selenium and these prognostic factors lend further support to the likelihood that hepatic selenium deficiency is not just an isolated abnormality in alcoholic liver disease, but contributes to its pathogenesis. Hepatic abnormalities provoked by selenium deficiency represent an important link, synergistically joining the nutritional and hepatotoxic background of alcoholic liver injury and cirrhosis (12, 30).

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