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The Relationship Between Serum Malondialdehyde and Ceruloplasmin in Chronic Liver Disease

[Kronik Karaciğer Hastalığında Serum Malondialdehit ve Seruloplasmin Arasındaki İlişki]

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ABSTRACT

Oxygen free radicals play an important role in the pathogenesis of tissue damage in many pathological conditions, including liver diseases. The present study aims to investigate the possible relationship between serum malondialdehyde level, an index of lipid peroxidation, and ceruloplasmin level, a protective agent against lipid peroxidation, in chronic liver disease. A total of 65 consecutive patients enrolled in the study were divided into three subgroups consisted of 20 liver cirrhosis patients with ascites, 25 liver cirrhosis cases without ascites and 20 patients with various types of chronic hepatitis. Control group consisted of 20 healthy subjects. Serum malondialdehyde and ceruloplasmin levels, and routine biochemical analyses were assayed. The mean serum malondialdehyde level of the group 1 was found to be significantly higher than that of the group 2 ($p<0.01$) and also the mean serum malondialdehyde level was found to be higher in groups 1, 2 and 3 than that in the control group ($p<0.0001$ for all groups). There was no significant differences in any of these groups with respect to serum ceruloplasmin levels. It was found that there was an inverse relationship between serum malondialdehyde and albumin values in all groups. No correlation was found between the serum ceruloplasmin and malondialdehyde contents and serum aspartate aminotransferase, alanine aminotransferase, total bilirubin and total protein concentrations. It was found that serum malondialdehyde level was significantly higher in patients with chronic hepatitis and liver cirrhosis than that of the control subjects whereas the serum ceruloplasmin level din't alter in any of the study groups. No correlation was detected between the serum malondialdehyde and ceruloplasmin levels in patients with chronic liver disease. It was suggested that increase in the serum malondialdehyde level might be associated with an imbalance of other antioxidants rather than ceruloplasmin in chronic liver diseases.

Key Words: malondialdehyde, ceruloplasmin, cirrhosis, hepatitis

ÖZET

Serbest oksijen radikalleri, karaciğer hastalıkları gibi birçok patolojik durumda doku hasarının patogenezinde rol oynamaktadır. Bu çalışma, kronik karaciğer hastalığında lipid peroksidasyonunun bir indeksi olan malondialdehit ile lipid peroksidasyonuna karşı koruyucu olduğu öne sürülen seruloplazminin serum değerleri arasındaki olası ilişkinin araştırılması amaçlandı. Çalışma kapsamına alınan 65 hasta üç alt gruba ayrıldı. Grup 1; asitli 20 karaciğer sirozlu hasta, grup 2; asitsiz 25 karaciğer sirozlu hasta, ve grup 3; çeşitli tiplerde kronik hepatiti olan 20 hasta içermekte idi. Kontrol grubunu 20 sağlıklı kişi oluşturdu. Serum malondialdehit, seruloplasmin ve rutin biyokimyasal ölçümler yapıldı. Grup 1 de ortalama serum malondialdehit seviyesi grup 2 den daha yüksekti ($p<0.01$) ve ayrıca grup 1, 2 ve 3 de kontrol grubundan daha yüksekti ($p<0.0001$ tüm gruplar için). Serum seruloplasmin açısından gruplarda önemli bir farklılık yoktu. Grupların tümünde serum malondialdehit ile albumin seviyeleri arasında ters ilişki bulundu. Serum malondialdehit ve seruloplasmin seviyeleri ile aspartat aminotransferaz, alanin aminotransferaz, total bilirübin ve total protein arasında herhangi bir korelasyon gözlenmedi. Kronik hepatitli ve karaciğer sirozlu hastalarda serum malondialdehit seviyelerinin yükseldiğini ancak seruloplasminde bir değişiklik olmadığı görüldü. Ayrıca bu hastalarda serum seruloplazmin ve malondialdehit düzeyleri arasında ilişki bulunamadı. Malondialdehit düzeyindeki artışın seruloplasminden başka antioksidanlardaki dengesizlikle ilişkili olabileceği öne sürüldü.

Anahtar Kelimeler: Malondialdehit, seruloplazmin, siroz, hepatit

INTRODUCTION

Oxygen free radicals play an important role in pathogenesis of tissue damage in many liver diseases. Free radicals such as superoxide and hydroxyl radicals, can cause a damage in cellular components via peroxidation of proteins, nucleic acids, free amino acids, and lipoproteins (1). Lipid peroxidation is caused by free radicals leading to oxidative destruction of polyunsaturated fatty acids constitutive of cellular membranes and to the production of toxic and reactive aldehyde metabolites such as malondialdehyde (MDA) which is commonly used as an index of lipid peroxidation (2). MDA can also initiate the formation of protein-aldehyde adducts (3). They are seen predominantly in the perivenous region and they coincide with sings of more advanced liver injury (steato-necrosis, focal inflammation, and elevated serum transaminases) (4). It has been reported that patients with degenerative liver disease had increased lipoperoxide levels in liver tissue and serum (5).

Antioxidant activity of the human serum has been attributed to the presence of transferrin and ceruloplasmin (CP). It has been suggested that CP might be the major antioxidant in plasma as a scavenger of oxygen radicals (6). However, there is controversion about the serum CP levels of patients with liver diseases. It was previously reported that lipid peroxidation has been found unchanged in moderate and severe alcoholic liver cirrhosis (7) or decreased in chronic liver disease (8). These data may be interpretated to indicate a relationship between CP and lipid peroxidation in liver cirrhosis. Therefore, we aimed to investigate the MDA and CP levels in serum of patients with chronic liver disease to compare the ones in the serum of healthy controls in order to estimate the possible relationship between serum MDA and CP levels in those subjects.

MATERIAL and METHODS

In a recent report, McColl et al. investigated the prevalence of the FVL, Pt20210, and MTHFR mutations in the etiology of stroke in 50 children at two centers (7)**.** Excluding the 11 neonatal cases, the median age at which stroke occurred was 51 months (range, 10-168 months). Most of the patients had hemiparesis, and had no family history of cerebrovascular disease at a young age. Of the 50 cases, only 37 were evaluated for the for the detailed analysis. The authors found that 2 children were heterozygous for the FVL mutation, One patient was heterozygous for the Pt20210 mutation, 7 patients were homozygous for the MTFHR gene mutation, and 13 patients were heterozygous for this alteration. Compared to the findings in random, unselected, cord-blood controls, the patients who carried one of these mutations did not have a significantly higher odds ratio for stroke. The authors concluded that thrombophilia did not appear to play a significant role in the etiology of stroke in children. In contrast to the reports demonstrated that thrombophilia might be an important contributor to this condition. Zenz at al.(8) detected that 5 of 33 children as heterozygous for the FVL mutation. One of them was reported as homozygous whereas the other one was found to be heterozygous for the Pt20210 mutation Although they found no significant difference between the prevalence of Pt20210 mutation in the study group and that in the general population of Austria, the data identified FVL mutation as a possible risk factor for acute stroke after the neonatal period. Nowak-Göttl et al. (9) compared the findings in 148 children aged 0.5-16 years who had suffered spontaneous ischemic stroke to findings in 296 age-matched controls and identified elevated lipoprotein (a) level, FVL, Pt20210 and MTHFR mutations as important risk factors for spontaneous ischemic stroke in childhood. The odds ratios for the FVL and the Pt20210 mutations were reported as 6 and 4.7, respectively. However, the authors noted that the presence of an additional risk factor increased the odds ratio significantly. The patient's history did not reveale a previous infection as a risk factor. In addition, there were no underlying issues such as cardiac disorder, intracardiac thrombus, or vasculitic disease. We suggest that the thrombosis in our patient was a spontaneous event that was facilitated by FVL. We also conclude that thrombophilic mutations should be kept in mind in the etiology of acute stroke.

RESULTS

As seen in Table 2, the mean serum MDA level in group 1 was significantly higher than that in group 2 ($p<0.01$); the mean serum MDA level was higher in groups 1, 2 and 3 than in the control group ($p<0.0001$ for all groups). There was no significant differences in any of these groups in terms of serum CP. It was found that there was an inverse relationship between serum MDA and albumin levels ($r=-0.56$, $p=0.010$; $r=-0.53$, $p=0.006$; $r=-0.53$, $p=0.016$ and $r=-0.55$, $p=0.012$ in groups 1, 2, 3 and controls respectively). There was no correlation between serum AST, ALT, T bil, T prot and CP and MDA levels.

DISCUSSION

Lipid peroxidation, a free radical-induced mechanism, is implicated in the pathogenesis of several acute and chronic human disorders, including liver pathology (10). Either exposure to more oxidant stress or an inability in the oxidative capacity of the cells might lead to acceleration of peroxidation reactions of some cellular molecules including lipids (11). Early stimulation of stellate cells, which are the major source of extracellular matrix, by lipid peroxides in vivo may be important in many forms of liver fibrosis. In situ studies show a correlation between the presence of aldehyde adducts and collagen gene expression by stellate cells (12,13), and peroxides stimulate collagen synthesis by cultured stellate cells (14). Activation of stellate cells is provoked by generation of free radicals in culture and is blocked by some antioxidants (15). The increase in lipid peroxidation has been previously reported in various liver diseases (16-18) suggesting that antioxidant levels were typically depleted in cirrhotic liver, which could also amplify the injurious effects of lipid peroxides (19). It has been also found that high serum levels of MDA in patients with liver cirrhosis was correlated with lower serum levels of vitamin E (20). Our data confirms the presence of an increased oxidative stress in cirrhosis and hepatitis cases. These findings suggest that such patients are under oxidant stress resulting from liver failure or inflammation, and more oxidative stress could happen as liver disease progresses.

Table 1 Demographic characteristics of the study subjects.

	Group 1	Group 2	Group 3	Control
Number	20	25	20	20
Sex (male/female)	16/4	20/5	12/8	15/5
Age (years)	53.25±11.95	48.56±13.62	38.30±10.84	46.70±10.34
HBV carrier	12	11	10	-
HCV carrier	-	3	8	-
HBV+HCV carrier	1	1	-	-
HBV+HDV carrier	1	-	2	-
Others (cryptogenic or alcholic)	6	10	-	-

Table 2 Routine liver function tests, serum MDA and CP levels.

	Group 1	Group 2	Group 3	Control
AST (U/L)	90.75±50.43[a,c]	84.60±66.92[a,c]	55.25±42.23[b]	15.5±4.79
ALT (U/L)	78.00±74.34[b]	64.52±37.76[c]	101.60±85.10[a]	29.80±6.84
T Bil (mg/dl)	2.19±3.42	2.42±3.45[b,c]	0.88±0.71	0.61±0.20
T Prot (g/dl)	6.36±0.78[d]	7.34±0.94	7.51±0.64	7.49±0.53
Albumin (g/dl)	2.70±0.26[a,e,f]	3.25±0.61[a,f]	4.11±0.45	4.36±0.40
MDA (μmol/l)	21.10±6.97[a,e]	16.52±5.85[a]	19.20±5.11[a]	5.61±0.99
CP (mg/dl)	33.69±8.70	33.95±13.84	31.87±9.86	38.49±10.42

Results were expressed as the mean±SD.
a; p<0.0001: compared with control; b, p<0.05: compared with group 4;
c,p<0.05: compared with group 3; d, p<0.0001 compared with the other groups;
e, p<0.01 compared with group 2; f, p<0.0001 compared wirh group 3.

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