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Dynamic thiol-disulfide homeostasis is disturbed in hepatitis B virus-related chronic hepatitis and liver cirrhosis

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Background/aim: Thiol-disulfide homeostasis is an important antioxidant defense mechanism. This study was conducted to investigate dynamic thiol-disulfide homeostasis in patients with hepatitis B virus-related chronic hepatitis and liver cirrhosis.

Materials and methods: Seventy-one treatment-naive patients with chronic hepatitis B (CHB), 50 patients with hepatitis B virus-associated liver cirrhosis, and 45 healthy controls were included in the study. Serum total and native thiol concentrations and serum disulfide concentrations were measured using an automated method.

Results: Mean serum total thiol concentrations in the control, CHB, and cirrhosis groups were 481.64 ± 37.87 μmol/L, 438.50 ± 71.35 μmol/L, and 358.07 ± 80.47 μmol/L, respectively ($P < 0.001$), and mean serum native thiol concentrations in the control, CHB, and cirrhosis groups were 452.92 ± 36.43 μmol/L, 400.16 ± 65.92 μmol/L, and 328.15 ± 74.91 μmol/L, respectively ($P < 0.001$). Mean serum disulfide concentrations in the control, CHB, and cirrhosis groups were 14.38 ± 3.38 μmol/L, 19.19 ± 6.16 μmol/L, and 14.98 ± 5.53 μmol/L, respectively ($P < 0.001$). There was a progressive decrease in both mean serum native and total thiol concentrations parallel to the liver fibrosis stage.

Conclusion: : Thiol-disulfide homeostasis is disturbed in patients with hepatitis B virus-related chronic hepatitis and liver cirrhosis.

Key words: Hepatitis B, thiols, disulfides, oxidative stress

1. Introduction

Hepatitis B is an important healthcare problem. It is estimated that global prevalence of hepatitis B is around 3.6% (1). Hepatitis B virus (HBV) causes a wide spectrum of liver diseases ranging from inactive chronic carrier state to end-stage liver disease and it is one of the most important causes of hepatocellular carcinoma (HCC) worldwide. The pathogenesis of chronic hepatitis B is complex. Rather than the cytopathic effect of HBV itself, hosts' immune responses are shown to play key roles in viral persistence and hepatocellular necroinflammation. Several complex interactions involving viral factors, hepatocytes, nonparenchymal liver cells, and inflammatory cells have been described during the course of HBV-related liver diseases (2). Several cytokines have also been shown to be important in the pathogenesis of viral persistence, hepatocellular inflammation, and fibrosis (3–5). There are also a number of studies in the literature reporting that oxidative stress may also contribute to the pathogenesis of hepatocellular damage associated with HBV-related chronic liver diseases (6–8). Oxidative stress has also been implicated in the pathogenesis of HCC (9,10).

The human body is continuously exposed to oxidative stress due to various reasons; therefore, it is essential for the body to maintain effective antioxidant defense mechanisms. Thiols are a group of compounds that contain sulfhydryl groups in their structures. They are one of the most important defense mechanisms against oxidative stress. Oxidative stress leads to the formation of reversible disulfide bonds between protein thiols and other low-molecular-weight thiols, particularly with glutathione. This process, so-called S-thiolation, has regulatory effects on protein function (redox regulation) while simultaneously protecting it from higher states

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of irreversible oxidation. Due to the reversible nature of S-thiolation, reduced protein thiols can be regenerated from their S-glutathionylated forms using various enzymes such as disulfide isomerase, mitochondrial glutaredoxin, or thioredoxin. These reactions maintain the dynamic thiol-disulfide homeostasis and it is strictly controlled in vitro. Besides being important for antioxidant defense, thiol-disulfide homeostasis has also been shown to be important for redox regulation of cell signaling and apoptosis (11,12). Recently, Erel and Neselioglu developed a novel, simple, and automated method to measure serum total thiol, native thiol, and disulfide concentrations allowing accurate determination of serum dynamic thiol-disulfide homeostasis (13). Using this novel method, disturbances in dynamic thiol-disulfide homeostasis were shown in several diseases (14–17). As previously stated, oxidative stress has also been implicated to contribute to the pathogenesis of HBV-related chronic liver diseases and HCC. In this context, the current study was conducted to investigate dynamic thiol-disulfide homeostasis in patients with HBV-associated chronic liver diseases.

2. Materials and methods

Seventy-one treatment-naive patients with chronic hepatitis B (CHB), 50 patients with HBV-associated liver cirrhosis, and 45 healthy controls were included in the study. The study protocol was approved by the local ethics committee of the Necmettin Erbakan University Faculty of Medicine and written informed consent was received from all the participants. The CHB group consisted of patients who were positive for hepatitis B surface antigen (HBsAg) for at least 6 months with active viral replication (HBV DNA > 2000 IU/mL). Liver biopsy was performed for every subject in the CHB group and the Ishak scoring system was used for grading necroinflammation and fibrosis (18). The cirrhosis group, on the other hand, consisted of HBsAg-positive patients for whom cirrhosis was diagnosed either by liver biopsy (Ishak stage 5 and 6 fibrosis) or on the basis of clinical, laboratory, and radiological findings. Finally, the control group consisted of 45 healthy people with normal liver enzymes and negative serological tests for hepatitis B and C (HBsAg, hepatitis B core antibody, anti-HCV antibody). Exclusion criteria were as follows: patients with chronic liver diseases of any other etiology, patients with considerable alcohol consumption (>20 g/day for men and >10 g/day for women), and patients with known malignancies, chronic renal diseases, autoimmune diseases, or any active ongoing infections. Serum samples were obtained early in the morning after overnight fasting. Serum samples in CHB and cirrhosis groups were obtained prior to the initiation of antiviral therapy. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) activities as well as other biochemical parameters were measured using standard autoanalyzers. Serum samples for thiol-disulfide homeostasis analyses were obtained by centrifugation for 5 min at 4 °C and 4000 rpm and were transferred to a freezer to be stored at −80 °C. All samples were analyzed later the same day. As previously mentioned, dynamic thiol-disulfide homeostasis parameters were measured using Erel and Neselioglu's method as follows: first, sodium borohydride is added to the serum sample to reduce all dynamic disulfide bonds to functional thiols. Then formaldehyde is added to the milieu in order to remove the excess of unconsumed sodium borohydride. The total thiol concentration is measured using modified Ellman reagent. Native thiol concentration is subtracted from the total thiol concentration and half of the obtained difference gives the disulfide bond amount.

Statistical analyses of the study were done using SPSS 19.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation. Continuous variables were tested for normal distribution using the one-sample Kolmogorov–Smirnov test. Comparisons for more than two groups were done with one-way ANOVA (normally distributed parameters) and the Kruskal–Wallis test (nonnormally distributed parameters). Student's t-test and the Mann–Whitney U test were used to test the significance of the differences between two groups for normally and nonnormally distributed parameters, respectively. The significance of the linear correlation between continuous variables was tested using the Pearson correlation coefficient test. Receiver operating characteristic (ROC) curves were obtained for tested parameters to predict severe inflammation and advanced fibrosis. Sensitivity, specificity, and positive and negative predictive values were calculated for specified cutoff values. Statistical significance for all analyses was defined as $P < 0.05$.

3. Results

The study group consisted of 71 (42.8%) treatment-naive CHB patients, 50 patients (30.1%) with HBV-associated liver cirrhosis, and 40 (27.1%) healthy controls. Sex distribution was found to be similar in the study groups ($P = 0.06$). Mean age, on the other hand, was found to be significantly higher in the cirrhosis group than in the CHB and control groups (48.73 ± 7.37, 46.70 ± 13.64, and 57.88 ± 9.91 years for control, CHB, and cirrhosis groups respectively; $P < 0.001$). All patients in the CHB group were positive for anti-HBe antibody. Demographical characteristics and laboratory findings of the study groups are summarized in Table 1.

Mean serum total thiol concentrations in the control, CHB, and cirrhosis groups were 481.64 ± 37.87 μmol/L,

Table 1. Clinical, demographical, and laboratory data and dynamic thiol-disulfide homeostasis parameters in the study groups.

	Control group (n = 45)	Chronic hepatitis B (n = 71)	Cirrhosis (n = 50)	P
Age (years)	48.73 ± 7.37 a	46.70 ± 13.64 a	57.88 ± 9.91 b	<0.001
Male (n, %) / female (n, %)	23 (51.1) / 22 (48.9)	38 (53.5) / 33 (46.5)	36 (72) / 14 (28)	0.064
Creatinine (mg/dL)	0.76 ± 0.13	0.75 ± 0.12	0.77 ± 0.24	0.997
ALT (U/L)	20.87 ± 8.8 a	45.16 ± 43.01 b	36.49 ± 30.97 b	0.002
AST (U/L)	17.30 ± 7.75 a	33.67 ± 23.86 b	48.34 ± 41.40 c	<0.001
GGT (U/L)	19.53 ± 10.75 a	31.44 ± 27.11 b	74.50 ± 85.83 c	<0.001
ALP (U/L)	65.04 ± 13.68 a	83.79 ± 29.13 b	111.73 ± 54.33 c	<0.001
T.Bil (mg/dL)	0.73 ± 0.35 a	0.96 ± 0.58 b	2.84 ± 4.14 c	<0.001
D.Bil (mg/dL)	0.24 ± 0.13 a	0.45 ± 1.24 a	1.41 ± 2.51 b	0.004
Albumin (g/dL)	4.43 ± 0.25 a	4.31 ± 0.36 a	3.34 ± 0.66 b	<0.001
Hemoglobin (g/dL)	14.36 ± 1.67 a	15.14 ± 7.5 a	11.64 ± 2.57 b	0.001
Leukocytes (mm^3)	6.92 ± 1.48 a	7.05 ± 1.83 a	5.11 ± 2.32 b	<0.001
Thrombocytes (mm^3)	252.58 ± 50.84 a	258.71 ± 150.74 a	105.22 ± 62.62 b	<0.001
Native thiol (μmol/L)	452.92 ± 36.43 a	400.16 ± 65.92 b	328.15 ± 74.91 c	<0.001
Total thiol (μmol/L)	481.64 ± 37.87 a	438.50 ± 71.35 b	358.07 ± 80.47 c	<0.001
Disulfide (μmol/L)	14.38 ± 3.38 a	19.19 ± 6.16 b	14.98 ± 5.53 a	<0.001
SS/SH%	3.18 ± 0.79 a	4.83 ± 1.44 b	4.64 ± 1.60 b	<0.001
SS/total thiol%	2.98 ± 0.69 a	4.38 ± 1.16 b	4.20 ± 1.32 b	<0.001
SH/total thiol%	94.03 ± 1.37 a	91.25 ± 2.33 b	91.58 ± 2.65 b	<0.001

ALT: Alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyltransferase, ALP: alkaline phosphatase, T.Bil: total bilirubin, D.Bil: direct bilirubin, SS: disulfide, SH: native thiol.
Letters a, b, and c denote binary comparisons between the groups. The difference between the groups is statistically significant if marked with different letters.

438.50 ± 71.35 μmol/L, and 358.07 ± 80.47 μmol/L, respectively, and the difference between the groups was statistically significant (P < 0.001). Intergroup comparisons showed that mean serum total thiol concentrations in both the CHB (P < 0.001) and cirrhosis groups (P < 0.001) were significantly lower than in the control group, and the cirrhosis group also had significantly lower mean serum total thiol concentration than the CHB group (P < 0.001).

Mean serum native thiol concentrations in the control, CHB, and cirrhosis groups were 452.92 ± 36.43 μmol/L, 400.16 ± 65.92 μmol/L, and 328.15 ± 74.91 μmol/L, respectively, and the difference between the groups was also statistically significant (P < 0.001). Intergroup comparisons showed that mean serum native thiol concentrations in both the CHB (P < 0.001) and cirrhosis groups (P < 0.001) were significantly lower than in healthy controls and the cirrhosis group also had significantly lower mean serum total thiol concentration than the CHB group (P < 0.001).

Mean serum disulfide concentrations in the control, CHB, and cirrhosis groups were 14.38 ± 3.38 μmol/L, 19.19 ± 6.16 μmol/L, and 14.98 ± 5.53 μmol/L, respectively, and statistical analyses revealed that the CHB group had significantly higher mean serum disulfide concentration than both the control (P < 0.001) and cirrhosis groups (P < 0.001), but the difference between the control and cirrhosis groups was not statistically significant (P = 0.54).

Mean serum native thiol, total thiol, and disulfide concentrations in the CHB, cirrhosis, and control groups are summarized in Figure 1.

Mean native thiol/total thiol, disulfide/total thiol, and disulfide/native thiol ratios in the control, CHB, and cirrhosis groups are given in Table 1. Statistical analyses showed that both disulfide/total thiol and disulfide/native thiol ratios were significantly higher and native thiol/total thiol ratio was significantly lower in the CHB and cirrhosis groups when compared to healthy controls.

In order to search for the association of thiol-disulfide homeostasis with the degree of liver fibrosis, patients in the CHB group were divided into 2 subgroups according to liver biopsy findings: mild fibrosis (Ishak stages 1 and 2) and moderate fibrosis (Ishak stages 3 and 4). There were

45 (63.4%) patients in the mild fibrosis and 26 (36.6%) patients in the moderate fibrosis group. The cirrhosis group was also included in the analyses as the advanced fibrosis group. Findings are summarized in Table 2. As can be seen, there was a significant progressive decrease in both mean serum native thiol and total thiol concentrations in parallel to the liver fibrosis stage and serum native thiol and total thiol concentrations were lowest in patients with advanced fibrosis (cirrhosis). Mean serum disulfide concentration was also significantly different among mild, moderate, and advanced fibrosis groups; both moderate and advanced fibrosis groups had significantly lower mean serum disulfide concentrations than the mild fibrosis group. Mean serum disulfide concentration was also lower in the advanced fibrosis group than in patients with moderate fibrosis, but the difference was not statistically significant (P = 0.11).

Liver biopsies were available for 73 patients (71 patients in the CHB group and 2 patients in the cirrhosis group). According to the degree of inflammation in liver biopsy samples, patients were grouped into three categories: mild inflammation (Ishak HAI: 1–8), moderate inflammation (Ishak HAI: 9–18), and severe inflammation (Ishak HAI: 19–24). There were 34 (46.6%) patients with mild inflammation, 23 (31.5%) patients with moderate inflammation, and 16 (21.9%) patients with severe inflammation. Mean serum native thiol, total thiol, and disulfide concentrations were found to be higher in the mild inflammation group when compared to the moderate and severe inflammation groups. Findings are summarized in Table 3.

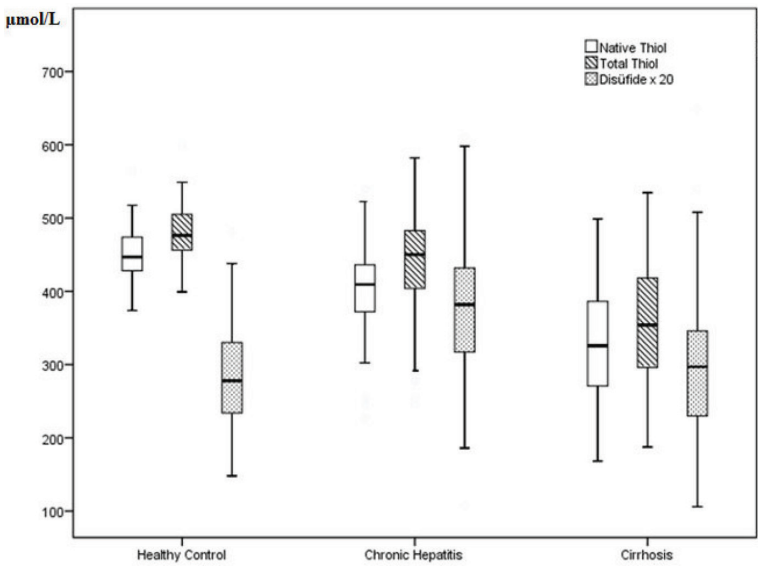

Figure 1. Mean serum native thiol, total thiol, and disulfide concentrations in chronic hepatitis B, cirrhosis, and control groups.

Table 2. Dynamic thiol-disulfide homeostasis parameters in patients with mild and moderate fibrosis and cirrhosis.

	Chronic hepatitis B with mild fibrosis (Ishak stage 1–2) (n = 45)	Chronic hepatitis B with moderate fibrosis (Ishak stage 3–4) (n = 26)	Cirrhosis (n = 50)	P
Native thiol (µmol/L)	414.08 ± 61.46 a	376.08 ± 67.58 b	328.15 ± 74.91 c	<0.001
Total thiol (µmol/L)	454.77 ± 65.67 a	410.37 ± 73.24 b	358.07 ± 80.47 c	<0.001
Disulfide (µmol/L)	20.37 ± 6.20 a	17.16 ± 5.64 b	14.98 ± 5.53 b	<0.001
SS/SH%	4.97 ± 1.45 a	4.60 ± 1.43 b	4.64 ± 1.60 b	0.493
SS/total thiol%	4.49 ± 1.14	4.18 ± 1.19	4.20 ± 1.32	0.450
SH/total thiol%	91.03 ± 2.29	91.63 ± 2.40	91.58 ± 2.65	0.474

SS: Disulfide, SH: native thiol.
Letters a, b, and c denote binary comparisons between the groups. The difference between the groups is statistically significant if marked with different letters.

There were 24 (48.0%) patients with compensated and 26 patients (52.0%) with decompensated cirrhosis in the cirrhosis group. Decompensation was defined as the development of ascites, variceal bleeding, or hepatic encephalopathy. Table 4 summarizes mean serum native thiol, total thiol, and disulfide concentrations in the compensated and decompensated patients. Mean serum native thiol, total thiol, and disulfide concentrations were found to be significantly lower in patients with decompensated cirrhosis when compared to patients with compensated cirrhosis.

Healthy controls were excluded from the analyses and ROC curves were obtained for serum total thiol, native thiol, and disulfide concentrations to differentiate the advanced fibrosis group from patients with mild and moderate fibrosis. For total thiol, the AUC was 0.779 (95% CI: 0.695–0.864) and the specified cut-off value of 419.40 μmol/L yielded 78.0% sensitivity and 69.0% specificity. For native thiol, the AUC was 0.768 (95% CI: 0.681–0.855) and the specified cut-off value of 388.65 yielded 80.0% sensitivity and 64.8% specificity. Lastly, for disulfide, the AUC was 0.728 (95% CI: 0.634–0.822) and the specified cut-off value of 16.30 yielded 72.0% sensitivity and 70.0% specificity. ROC curves are summarized in Figure 2.

Regression analysis was performed to determine independent factors affecting serum thiol-disulfide parameters in patients with CHB and liver cirrhosis. Fibrosis stage and age were found to be independently associated with serum total and native thiol concentrations. On the other hand, age was not an independent factor in terms of serum disulfide concentration and only fibrosis stage was identified as an independent factor affecting serum disulfide concentration. Regression analyses are summarized in Table 5.

4. Discussion

Free radicals, reactive oxygen, and nitrogen species are continuously generated in the body as byproducts of several physiological processes such as mitochondrial oxidative phosphorylation, catabolism of lipids, amino acids, or exogenous molecules such as drugs. These substances are highly reactive and have hazardous effects on several macromolecules within the cell, such as DNA, proteins, and lipids, causing serious disturbances in

Table 3. Dynamic thiol-disulfide homeostasis parameters in patients with mild, moderate, and severe inflammation in liver biopsies.

	Mild inflammation (n = 34)	Moderate inflammation (n = 23)	Severe inflammation (n = 16)	P
Native thiol (μmol/L)	424.91 ± 50.18 a	383.37 ± 71.62 b	354.98 ± 69.12 b	0.003
Total thiol (μmol/L)	467.01 ± 53.64 a	417.83 ± 75.94 b	389.62 ± 76.13 b	0.001
Disulfide (μmol/L)	21.07 ± 6.63 a	17.24 ± 4.44 b	17.34 ± 6.11 b	0.014
SS/SH%	4.99 ± 1.56	4.56 ± 1.17	4.91 ± 1.51	0.642
SS/total thiol%	4.51 ± 1.22	4.17 ± 0.99	4.44 ± 1.22	0.661
SH/total thiol%	90.99 ± 2.45	91.67 ± 1.99	91.23 ± 2.31	0.654

SS: Disulfide, SH: native thiol.
Letters a, b, and c denote binary comparisons between the groups. The difference between the groups is statistically significant if marked with different letters.

Table 4. Dynamic thiol-disulfide homeostasis parameters in patients with compensated and decompensated cirrhosis.

	Compensated cirrhosis (n = 24)	Decompensated cirrhosis (n = 26)	P
Native thiol (μmol/L)	364.65 ± 63.74	294.46 ± 69.72	0.001
Total thiol (μmol/L)	397.46 ± 65.92	321.72 ± 76.37	0.001
Disulfide (μmol/L)	16.43 ± 4.41	13.64 ± 6.18	0.032
%SS/SH	4.60 ± 1.38	4.68 ± 1.81	0.847
%SS/total thiol	4.17 ± 1.13	4.24 ± 1.51	0.868
%SH/total thiol	91.63 ± 2.27	91.53 ± 3.01	0.885

SS: Disulfide, SH: native thiol.

various cellular functions. Since the liver is the major organ for several synthetic and detoxification reactions, it is continuously exposed to oxidative stress. Therefore, the oxidant/antioxidant balance is of particular importance for the liver to function properly.

Oxidative stress has been implicated in the pathogenesis of several chronic liver diseases, particularly fatty liver disease and nonalcoholic steatohepatitis (17,19,20). Oxidative stress has also been shown to contribute to the pathogenesis of HBV-related chronic liver diseases. Severy et al. (21) demonstrated that HBV replication induces oxidative stress in the Hep AD 38 cell line in vivo and there are several studies in the literature reporting that serum and tissue markers of oxidative stress are increased in

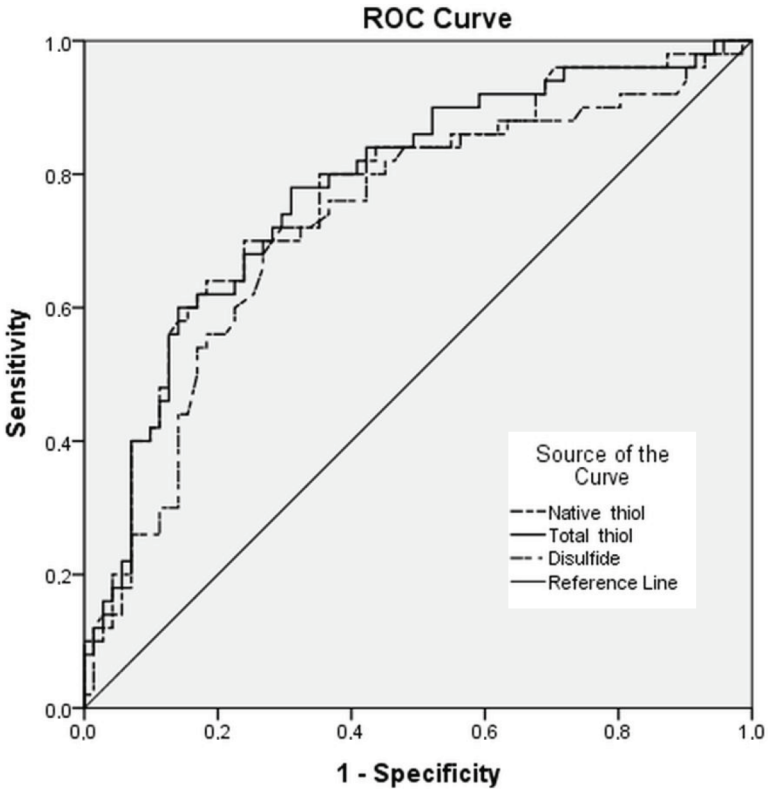

Figure 2. ROC curves for serum total thiol, native thiol, and disulfide concentrations to differentiate patients with advanced fibrosis from patients with mild and moderate fibrosis.

Table 5. Regression analysis for independent factors affecting serum thiol-disulfide parameters in patients with CHB and liver cirrhosis.

		B	β	95% CI		P
				Upper	Lower	
Fibrosis stage	Total thiol	–54.78	–0.35	–82.13	–27.44	<0.001
	Native thiol	–61.82	–0.36	–91.25	–32.38	<0.001
	Disulfide	–4.31	–0.34	–6.50	–2.13	<0.001
Age	Total thiol	–1.57	–0.27	–2.58	–0.56	0.003
	Native thiol	–1.71	–0.27	–2.8	–0.63	0.002
	Disulfide	NA	NA	NA	NA	0.112

B: Regression coefficient, *β*: standardized correlation coefficient, CI: confidence interval, NA: not applicable.

patients with HBV-related chronic liver diseases. Valgimigli et al. (22) reported that reactive oxygen species were significantly increased in liver samples of CHB patients when compared to healthy controls. In another study, serum and erythrocyte levels of malondialdehyde (MDA), which is a marker of lipid peroxidation, were shown to increase in patients with CHB and correlate with serum ALT and HBV DNA levels (23). MDA levels were also shown to correlate with MELD scores in CHB patients with acute chronic liver failure (24). Markers of protein and DNA oxidation were also shown to increase in serum and hepatocytes of CHB patients, which also supports the possible role of oxidative stress in the pathogenesis of CHB (10,25). In addition to the increase in markers of oxidative stress, there are studies in the literature reporting decreases in antioxidant markers in patients with HBV-associated chronic liver diseases (23,26).

Oxidative stress is also believed to participate in the pathogenesis of HBV-associated HCC. Poungpairoj et al. (27) reported that plasma protein carbonyl content was significantly higher and total antioxidant capacity was significantly lower in HBV-associated HCC patients when compared to healthy controls. The *HBx* gene and its associated protein are important in the pathogenesis of HBV-related carcinogenesis and in vitro studies have shown that they induce oxidative stress and mitochondrial DNA damage in cells (28).

The current study showed that dynamic thiol-disulfide homeostasis is disturbed and shifts towards the disulfide side in patients with HBV-associated chronic liver diseases, which indicates the presence of oxidative stress during the course of chronic HBV infection. In this context, our results are consistent with the prior studies in the literature, some of which were already mentioned above. According to the results of the current study, serum native and total thiol concentrations were found to be lower in CHB and cirrhosis patients when compared to healthy controls. Serum native and total thiol concentrations were also significantly lower in cirrhosis patients compared to noncirrhotic CHB patients, being lowest in patients with decompensated cirrhosis. These findings indicate that the decrease in serum native and total thiol concentrations in the course of CHB is progressive and it is parallel to the stage of the disease and parenchymal failure.

Our results also showed that mean serum disulfide concentrations differed significantly among the study groups, but the situation here was a bit more complex; although mean serum disulfide concentration was higher in patients with CHB compared to healthy controls, the same was not true for cirrhotic patients. We believe that this is due to the significant decrease in the serum albumin concentration in patients with cirrhosis. Albumin thiols constitute a significant amount of the plasma thiol pool; therefore, besides increased oxidative stress, decreased serum albumin levels also contribute to decreased serum total and native thiol concentrations in cirrhotic patients. In this context, the amount of thiols to be converted to disulfides would be low in cirrhotic patients, preventing serum disulfide levels from increasing further. As can be clearly seen from our results, although mean serum disulfide concentration was not different from that of healthy controls in cirrhotic patients, both disulfide/total thiol and disulfide/native thiol ratios were significantly higher in cirrhotic patients when compared to healthy controls, which also supports our hypothesis .

One of the strengths of the current study is that it includes a homogeneous group of patients with chronic liver disease of a uniform etiology, i.e. CHB. There are many patients with different stages of HBV-associated chronic liver disease and the sample size is decent for statistical comparisons. On the other hand, the cross-sectional design of the study constitutes the major limitation of the study. A prospective study with serial measurements of serum dynamic thiol-disulfide homeostasis parameters at different time points during the course of CHB would better clarify the changes in the dynamic thiol-disulfide homeostasis during the course of hepatitis B-related chronic liver diseases.

In conclusion, dynamic thiol-disulfide homeostasis is disturbed in HBV-related chronic liver diseases. This implies the possible role of oxidative stress in HBV-associated chronic liver injury. Further studies may clarify the exact role of oxidative stress and antioxidant defense mechanisms during the course of HBV-related chronic liver diseases and may facilitate development of novel treatment strategies.

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