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Changes of Plasma Biomarkers in Patients with Chronic Liver Diseases Predict Liver Cell Death

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1. Abstract

1.1. Background: We evaluated the changes of biomarkers and their significance in patients with nonalcoholic fatty liver disease.

1.2. Methods: One hundred and ten nonalcoholic fatty liver disease patients were enrolled into experimental group and one hundred and ten healthy people into control group. The plasma levels of biomarkers were detected.

1.3. Results: The level of biomarkers was significantly higher in the experimental group than that in the control group ($P<0.05$). The ALT, AST and UC measured values were significantly higher in patients with moderate liver steatosis and severe liver steatosis compared to those with mild fatty liver steatosis($P<0.05$). The plasma levels of FBG were negatively associated with LDL-C ($P<0.05$) and C1q ($P<0.05$) in FLD patients. The plasma levels of FBG were positively associated with GGT ($P<0.05$) in FLD patients.

1.4. Conclusions: The data demonstrate that plasma sensitive markers for early diagnosis of gut failure and possibility of FLD. The impairment of intestinal barrier function may be one of the critical reasons for deterioration of FLD.

2. Introduction

Chronic liver disease, which is a common cause of chronic liver disease, is characterized by hepatic fat accumulation. Based on the epidemiological evidence, the global prevalence of NAFLD has been estimated as high as one billion cases. The development of liver injury in NAFLD involves many stages, such as Triglyceride (TG) and free fatty acid accumulation in hepatocytes, oxidative stress, lipid peroxidation, mitochondrial dysfunction, liver inflammation, insulin resistance, and perturbations of adipokine levels. The pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD) is not yet fully understood; currently, researchers have proposed the 'two-hit' hypothesis. The 'first hit', which leads to the formation of NAFLD, refers to an increase in the level of Free Fatty Acid (FFA) in the adipocytes and a decrease in the oxidation of FFAs in the liver, resulting in the excessive accumulation of fat in the liver cells. The 'second hit' refers to the release of inflammatory cytokines and the increase in the level of oxidative stress in NAFLD and the consequent persistent damage to the liver.

Cell death is an important physiological or pathological phenomenon in the process of life activities. Ferroptosis is a newly discovered programmed mode of death, which is significantly different from other types of death, such as apoptosis, necrosis and autophagy, in terms of morphology, biochemistry and genetics [1]. Iron death plays an important role in the development of various diseases, such as Parkinson's disease, ischemia-reperfusion injury and tumor. Recent studies [2-5] have shown that iron death features, such as iron metabolism disorder and lipid peroxide accumulation to varying degrees, have been found in various liver diseases, and regulation of iron death can affect the course of liver disease. This study aims to summarize and evaluate the mechanism of iron death and its role and progress in liver disease, providing new ideas for the improvement of the diagnosis and treatment level of liver disease in the future.

The earliest iron death inducers, Erastin and Ras Selective Lethal compounds (RSL3), were identified using high-throughput screen-

ing techniques. It was found that apoptosis, necrosis and autophagy inhibitors could not inhibit cell death induced by either of them, whereas antioxidants and iron chelating agents could inhibit the process. It was subsequently confirmed that this mode of cell death was related to intracellular iron and free radicals (ROS) [6-7]. In 2012, Dixon et al. [1] named iron death as the mode of death characterized by iron dependence and lipid peroxides accumulation. The changes of mitochondria are the main morphological characteristics of iron death, including the decrease of mitochondria volume, the increase of membrane density and the decrease or disappearance of mitochondria. The biochemical characteristics of iron death include depletion of glutathione (GSH), inactivation of Glutathione Peroxidase 4(GXP4), and accumulation of lipid peroxides.

3. Subjects and Methods

3.1. Patients

One hundred and ten patients, aged 18–70 year, with iconography or biopsy evidence of FLD were recruited for the study, who had been treated at the Department of Gastroenterology, Zongnan Hospital December 2016 to December 2019, were studied, and one hundred and ten healthy volunteers served as controls. NAFLD patients met the following inclusion criteria: male; aged 18–70 years; NAFLD. Subjects were excluded if they had uncontrolled hypertension, serological markers of hepatitis B/C virus infection, autoimmune liver disease, alcoholic liver disease or potential causes of hepatic injury, steatosis, or fibrosis. Age-matched healthy subjects were included as a control group. The study was approved by the Ethics Committee of Zongnan Hospital and each patient provided informed consent.

3.2. Reagents and Methods

Venous blood samples were drawn after fasting; serum samples were separated and analyzed for lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and TG), fasting plasma glucose, Aspartate Aminotransferase (AST), alanine aminotransferase (ALT) within 48 hours. The level of biomarkers was measured using the enzymatic-spectrophotometric method and standard stock solution and Dlactic dehydrogenase were purchased from Sigma Chemical Company, USA. All biomarkers was detected using theo-diamisidine reagent method. The plasma biomarkers concentration was measured using the highly sensitive ELISA kit (Lengton,shanghai, China), operated according to the instructions.

3.3. Statistical Analysis

Results were expressed as mean ± SD. Student's t test, ANOVA and linear correlation analysis using SPSS software (17.0 edition) were used. Differences between groups of steatosis were analyzed using ANOVA for continuous variables. Spearman correlation coefficient test was used to analyze the relationship between variables. All P values presented are two-tailed, and values less than 0.05 are considered to indicate statistical significance.

4. Results

4.1. Clinical Characters

As shown in Table 1, a total of 110 biopsy-proven or iconography-proven NAFLD patients were enrolled in the present study, including 19 NASH patients with significant fibrosis. The characteristics general clinical characteristics, including AST, ALT, Systolic Blood Pressure (SBP), Diastole Blood Pressure (DBP), FPG, TC, TG, LDL-C, and GGT were significantly higher in NAFLD patients when compared with age-matched healthy control subjects of the patients ($P < 0.05$). There were no significant differences in terms of sex, age, fibrinogen, ESR, CRP, Cr and HDL-C between the two groups ($P > 0.05$).

Table 1: Main characteristics of the study groups

Characteristics	Controls	NAFLD
n	105	129
Age	40.35±15.64	42.78±14.15
Gender(male)	34	43
(female)	26	35
ALT	23.89±11.94	56.14±26.48*
AST	22.45±9.52	53.63±25.70*
FPG	4.36±1.44	5.84±1.84*
Triglycerides	1.81±1.20	3.56±3.32*
Total cholesterol	3.96±0.86	5.74±1.68*
LDL	2.64±0.88	3.45±1.41*
HDL	1.15±0.46	1.20±0.57
Cr	64.78±12.08	67.47±15.64
GGT	43.56±20.52	77.92±31.67*
Systolic BP (mmHg)	115.26 ± 15.83	120.23 ± 16.48
Diastolic BP (mmHg)	75.68 ± 10.71	79.42 ± 11.36
ESR	31.26 ± 20.65	33.54 ± 19.32

4.2. Changes of Plasma Biomarkers in Patients

The plasma levels of the biomarkers of two groups were detected in all individuals shown in Table 2. The plasma levels of Transferritin and Ferritin in different subgroups stratified by severity of steatosis are shown in Table 3. The plasma levels of Transferritin and Ferritin of the patients were significantly higher than those of the controls ($P<0.05$). The Transferritin and Ferritin and endotoxin measured values were significantly higher in patients with moderate liver steatosis and severe liver steatosis compared to those with mild fatty liver steatosis($P<0.05$). But there was no significant difference in Transferritin and Ferritin level between subgroup of moderate liver steatosis and subgroup of severe liver steatosis ($P> 0.05$).

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Table 2: The results of plasma biomarkers in patients with FLD (mean±SD)

Characteristics	Patient without liver cirrhosis (n=105)	Patient with liver cirrhosis (n=129)
Ferritin(ng/l)	129.14±17.86	141.18±20.42
Transferrin(g/l)	3.67±1.06	3.03±1.21*

Table 3: The results of plasma biomarkers in patients with FLD (mean±SD)

Characteristics	Patient without liver cirrhosis (n=105)	Patient with liver cirrhosis (n=129)
SOD(kU/l)	211.36±29.78	238.15±34.92
UEFA(umol/l)	734.67±68.31	828.26±75.36*

4.3. Correlation Analysis of the Biomarkers in Patients with Chronic Liver Diseases

In the simple correlation analysis of the whole data set, the plasma levels of biomarkers were analyzed according to other clinical characteristics indicated in Tables 4-6. The plasma levels of FBG were negatively associated with LDL-C (R = -.376, P = .041) and C1q (R = -.384, P = .038) in NAFLD patients (Table 5). As shown in Table 8, we found that the plasma levels of ferritin were positively associated with GGT (R = .363, P = .036) in patients. However, transferritin were not associated with other clinical characteristics as indicated in Table 9.

Table 4: The results of plasma biomarkers in patients with cirrhosis (mean±SD)

Characteristics	Patient without liver cirrhosis (n=105)	Patient with liver cirrhosis (n=129)
LDH	135.76±49.63	144.88±46.32
LDH1	44.06±16.35	47.35±18.21

Table 5: The results of plasma biomarkers of the study groups stratified by severity of steatosis

Characteristics	Normal (n=105)	Child Pugh-A (n=45)	Child Pugh-B (n=51)	Child Pugh-C (n=33)
Ferritin(ng/l)	129.14± 17.86	135.32± 18.10	140.45± 20.74	139.24± 25.18
Transferrin(g/l)	3.67±1.06	3.06±1.32	2.89±1.03*	2.83± 1.51*

Table 6: The results of plasma biomarkers of the study groups stratified by severity of steatosis between SOD and UEFA

Characteristics	Normal (n=105)	Child-Pugh-A (n=45)	Child-Pugh-B (n=51)	Child-Pugh-C (n=33)
SOD(kU/l)	211.36± 29.78	240.74± 33.92	251.16± 41.02	245.40± 38.17
UEFA(umol/l)	734.67± 68.31	836.56± 81.08*	766.23± 71.20	752.63± 69.32

Table 7: Correlation of the factors associated with plasma FBG levels

Characteristics	Control subjects (n=150) R(P value)	NAFLD patients (n=167) R(P value)
ALT	-.157 (.377)	-.009(.965)
AST	.031 (.862)	.207(.311)
GGT	-.118 (.506)	-.091(.664)
LDL	-.065 (.714)	-.110(.618)
HDL	-.120 (.499)	-.205(.386)
Triglycerides	.111 (.532)	-.016(.942)
Total cholesterol	-.027 (.880)	-.059(.788)

Table 8: Correlation of the factors associated with plasma Transferrin levels

Characteristics	Patient without liver cirrhosis (n=105)	Patient with liver cirrhosis (n=129)
ALT	.172 (.329)	-.144(.484)
AST	.005 (.977)	-.017(.934)
TBIL	-.117 (.511)	-.376(.031)
TP	.103(.742)	.298(.048)
ALB	.008(.942)	.153(.348)
GGT	.167 (.345)	.363(.036)

Table 9: Correlation of the factors associated with plasma Ferritin levels

Characteristics	Patient without liver cirrhosis (n=105)	Patient with liver cirrhosisv (n=129)
ALT	.136 (.444)	-.079(.701)
AST	−.188 (.287)	.047(.821)
TBIL	0.053	.176(.584)
TP	0.124	-.198(.516)
ALB	0.131	-.351(.041)
GGT	-.108 (.543)	-.255(.219)

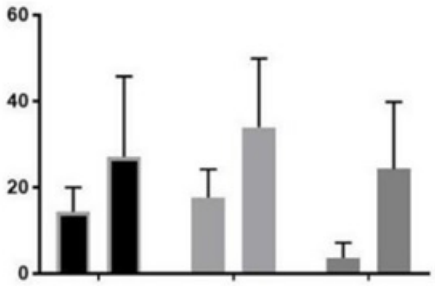

Figure 1: The plasma levels of biomarkers of the patients were significantly higher than those of the controls

5. Discussion

We found that these biomarkers were associated with chronic liver disease, characterized by hepatic fat accumulation and inmunne factors. Based on the epidemiological evidence, the global prevalence of NAFLD has been estimated as high as one billion cases. The development of liver injury in NAFLD involves many stages, such as Triglyceride (TG) and free fatty acid accumulation in hepatocytes, oxidative stress, lipid peroxidation, mitochondrial dysfunction, liver inflammation, insulin resistance, and perturbations of adipokine levels. The pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD) is not yet fully understood; currently, researchers have proposed the 'two-hit' hypothesis. The 'first hit', which leads to the formation of

NAFLD, refers to an increase in the level of Free Fatty Acid (FFA) in the adipocytes and a decrease in the oxidation of FFAs in the liver, resulting in the excessive accumulation of fat in the liver cells. The 'second hit' refers to the release of inflammatory cytokines and the increase in the level of oxidative stress in NAFLD and the consequent persistent damage to the liver.

Inactivation of GPX4 based on GSH consumption: As previously described, GPX4 is the only GPX (glutathione peroxidase) in the cell for liposome peroxidase reduction. The effect of GPX4 is reflected in that GPX4 can change the peroxide bond of lipid peroxidation into hydroxyl group and lose its peroxide activity. Based on the GPX. GPX4 inactivation: As described in 1, in addition to acting indirectly on GPX4-activating GSH, GPX4 can also be eliminated directly. Such as GPX4 inhibitors, squalene synthase, HMG-COA reductase. Iron ion input and iron ion reduction: Iron ions are input into cells and are ensured to exist in large quantities in the form of iron divalent. Iron divalent can initiate liposome peroxidation through Fenton reaction. Background Iron death is a non-apoptotic form of cell death that is dependent on the accumulation of iron in cells and leads to the elevation of toxic lipid peroxides ROS.

Iron death in a wide variety of disease plays an important role in the process of development, such as Parkinson's disease, ischemia-reperfusion injury, and tumors. , according to recent studies [2-51] in various liver diseases were found different degree of iron element metabolism and lipid peroxide concentration iron death characteristics, and regulation of iron death can affect the liver disease process. The purpose of this paper is to summarize and evaluate the mechanism of iron death and progress in the role of liver disease and liver disease diagnosis and treatment level of ascension for the future provide a new way.

Hereditary Hemochromatosis (HH) is an inherited systemic iron overload in which iron deposits in various organs produce ROS through the Fenton response, causing oxidative damage and ultimately leading to serious chronic complications including cirrhosis, diabetes, and heart disease. HH is characterized by an imbalance in iron regulation - iron transporter homeostasis, resulting in iron overload. Preclinical studies [19] have shown that iron overload in the liver can induce iron death in hepatocytes and macrophages in HH mouse models.

Alcoholic Liver Disease (ALD) is a liver disease caused by prolonged heavy drinking. Studies [20] showed that ALD patients had reduced serum ferritin, while divalent metal ion transporter expression increased in intestinal tract, resulting in increased serum iron and ferritin levels. Ethanol disrupts the activity of silencing regulatory protein 1(SIRT1). Yin et al. [21] found in a comparison between ethanol fed knockout SIRT1 mice and wild-type mice that knockout SIRT1 would aggravate lipid metabolism abnormalities and promote lipid peroxidation in the liver. These characteristics suggest that there are key characteristics of iron death in ALD patients. However, recent studies [2] suggest that intestinal SIRT1 inactivation can improve etho-induced iron homeostasis disorder in liver, thus improving alcoholic liver injury. It is believed that the liver protective effect of intestinal SIRT1 inactivation is related to the inhibition of iron death. This is contrary to the findings of Yin et al., and the relationship between ALD intestinal SIRT1 and iron death still needs further study.

Nonalcoholic Fatty Liver Disease (NAFLD) is a type of metabolic stress liver injury closely related to insulin resistance and genetic susceptibility. Nonalcoholic steatohepatitis (NASH) is an intermediate stage of progression from simple steatohepatitis to cirrhosis, and the underlying mechanisms underlying the transition from simple steatohepatitis to steatohepatitis remain unclear. At the beginning of 2020, an international expert panel composed of 30 experts from 22 countries released an international expert consensus on a new definition of metabolism-related fatty liver disease (MAFLD) [22], suggesting that "MAFLD" be used to replace "NAFLD". Based on the use of NAFLD in a large number of previous literatures, this title is still used in this paper. In the pathogenesis of NASH, oxidative stress caused by lipid peroxides accumulation is considered to be an important initiating factor, and iron deposition caused by metabolic disorders is also considered to be an aggravating factor of NASH. Therefore, iron death may be involved in the pathogenesis of NASH. Tsurusaki et al. [23] found that iron death inhibitors could inhibit the increase of ALT, AST and other markers of liver injury as well as TNFα, IL-6 and other inflammatory cytokines in the mice model of choline-deficient eTHOthine-rich diet, suggesting that iron death was the cause of the development of simple fatty liver into NASH. Subsequently, Li et al. [3] found in a mouse model of methionine choline deficiency diet that the characteristics of iron death included ROS aggregation, mitochondrial morphological changes and up-regulation of iron death-related genes, and inhibition of iron death could reduce liver injury, inflammation and even fibrosis in mice.

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