J Med Sci 2023;43(3):113-120
DOI: 10.4103/jmedsci.jmedsci_71_22

ORIGINAL ARTICLE

Inverse Association between Serum Iron and Liver Stiffness

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Background: Liver fibrogenesis is a process of hepatic cell repairment. Hepatic fibrosis is the pathological status of liver health under different stress, including infection or inflammation. Iron is an essential micronutrition with the specific function of human cells, while excess iron may induce oxidative stress in cells and tissues. **Aim:** The liver is the main organ of iron storage. The study aimed to evaluate the relationship of serum iron with the hepatic stiffness measurement (liver stiffness measurement [LSM]). **Methods:** A total of 5521 adult participants aged 20 and over with recorded LSM and serum iron concentration from the U. S. National Health and Nutrition Examination Survey datasets (2017–2018) were enrolled in this study. The association between serum iron concentration and LSM is analyzed by multivariate linear regression models. **Results:** An increased serum iron concentration was significantly correlated with decreasing LSM in the adjusted model (β coefficient: –0.0005; 95% confidence interval: –0.001, –0.00008; $P = 0.020$). Moreover, the subgroup analysis also disclosed a negative association in nongeriatric adults. The serum ferritin concentration was positively associated with LSM. The quartile-based analysis found a significant inverse correlation between quartile serum iron concentration and the lowest serum iron concentration. **Conclusion:** Serum iron concentration and LSM was inversely associated. The assessment of iron biomarkers might be a part of evaluating liver health and chronic liver diseases. Decrease serum iron or increase ferritin implies a possible pro-inflammatory process in the liver, and within the normal range, higher serum iron levels and lower serum ferritin are considered to be a balance status of body iron homeostasis and reduced the risks of liver fibrosis.

Key words: Serum iron, liver stiffness measurement, ferritin

INTRODUCTION

Iron is an essential element in human beings. It plays an important role in metabolism, especially in electron transfer reactions. Iron in the human body is present in hemoglobin, myoglobin, and many enzymes.[1] The storage forms of iron include ferritin and hemosiderin. Most of the iron flow into the plasma is generated by the release of iron recycled from senescent erythrocytes by splenic and hepatic macrophages.[2] Under normal circumstances, little iron is lost from the body. Modulating dietary absorption of iron regulates the total body content of iron. Hepcidin is the hormone that controls systemic iron homeostasis. It regulates serum iron levels, absorption of dietary iron, releasing iron from macrophages, and the storage of iron in the hepatocytes. Posttranscriptional regulation of key proteins involved in iron transport, storage, and utilization mainly maintains intracellular iron homeostasis.[3] Iron deficiency is a common nutritional disorder, and commonly related to iron-deficiency anemia. Excess iron or iron overload

Received: April 13, 2022; Revised: April 26, 2022; Accepted: May 03, 2022; Published: May 27, 2022
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How to cite this article: Cheng YW, Wu CJ, Sung CE, Hung CC, Kao HL, Chen WL. Inverse association between serum iron and liver stiffness. J Med Sci 2023;43:113-20.

results in iron storage disease, also in the term hemochromatosis, and hemosiderosis denotes an increase of tissue iron stores with or without tissue damage. Untreated hemochromatosis progress to organ damage clinically significant cirrhosis of the liver, darkening of the skin, diabetes, cardiomyopathies, and arthropathies.[4-6]

The liver is the largest organ in our body. Depending on its causes, liver disease can be acute or chronic and range from focal to diffuse and mild to severe. Acute liver disease is usually mild and recovers spontaneously. Patients with acute liver disease often complain of fatigue, poor appetite, and nausea, which are often misinterpreted as symptoms of other infectious diseases, and might have minor abnormalities seen through blood testing.[7] Liver injury may persist after the initial acute episode, and the results can be reversible or irreversible. Sometimes, the chronic liver disease results in stable liver function or complete resolution. Some cases result in liver function irreversible decline.[8] As the name implies, chronic liver disease is a combination of necrosis of hepatic cells and inflammation of varying severity persistent for more than 6 months. It may be due to viral infection, drugs, and toxins, genetic, metabolic, or autoimmune factors; or other unknown reasons. Hepatic fibrosis is characterized by changes in the cellular and matrix environment in the space of Disse. The activation of hepatic stellate cells (HSCs), extracellular matrix (ECM) immune cells, and lipocytes can occur liver damage progression. The ECM is replaced by a high-density matrix and ultimately progressed to cirrhosis of the liver. [7,9,10] Several noninvasive methods are used to assess the extent of fibrosis or hepatic tissue stiffness, such as the use of scoring systems through several laboratory tests and imaging methods.

Liver ultrasound transient elastography is an efficient and noninvasive way to measure the stiffness of liver tissue. Balanced iron homeostasis is quite important in the body in general healthy physiological status. The liver is considered one of the major storage organs of body iron and plays role in regulating iron homeostasis. This study aimed to figure out the correlation between serum iron and liver health in a generally healthy adult.

MATERIALS AND METHODS

Ethical approval

The NHANES was approved by National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB). All participants completed informed consent before analysis. Approval number: NHANES 2017-2018. Protocol #2018-01 (Effective beginning October 26, 2017). Continuation of Protocol #2011-17 (Effective through October 26, 2017).

Study participants

This study enrolled 5512 adult participants over 20 years of age in the U. S. National Health and Nutrition Examination Survey (NHANES) (2017–2018). Participants underwent measurements, including standardized interviews, physical examinations, and laboratory testing. The participants with missing data for body iron biomarkers (serum iron, ferritin, and total iron-binding capacity [TIBC]) concentrations, liver stiffness measurement (LSM), or other covariates were excluded from the study. The NHANES was approved by the National Center for Health Statistics Research Ethics Review Board. All participants completed informed consent before analysis.

Liver ultrasound transient elastography

The main goals of the liver ultrasound transient elastography are a measurement of two important liver diseases: liver fibrosis and hepatic steatosis. The examination was performed by well-trained and certified NHANES health technicians using the FibroScan® model 502 V2 Touch. FibroScan® is an ultrasound method with mechanical vibration of 50 Hz with mild amplitude and induces a shear wave through the liver. The velocity of the shear wave is associated with liver tissue stiffness. It is converted and expressed as LSM (kilopascals). FibroScan® is the Food and Drug Administration-approved technique for evaluating liver fibrosis. The examinations were performed followed the manufacturer's protocol.[11]

Measurement of serum iron, total iron-binding capacity, and ferritin

Serum iron concentration was measured by the University of Minnesota Advanced Research and Diagnostic Laboratory, Minneapolis. The Roche Cobas 6000 Chemistry Analyzer was used to measure the iron concentration. This is a three-step method using FerroZine reagent. Fe^{3+} is liberated from transferrin reduced to Fe^{2+} and finally forms a colored complex. To measure the unsaturated iron-binding capacity (UIBC), excess Fe^{2+} is added to the sample in the first step. In an alkaline environment, the unbound Fe^{2+} forms a colored compound with FerroZine reagent. The measurement occurs at 546 nm (secondary wavelength 700 nm). TIBC was the sum of serum iron and UIBC. The analytical measurement range of serum iron is 5–500 μg/dL, and UIBC is 17–700 μg/dL.[12,13]

Serum ferritin measurement was performed by the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis. The measurement used Electrochemiluminescence immunoassay "ECLIA" method on the Roche Cobas® e601 module. The Roche Diagnostics kit specifies expected values of 30–400 ng/mL for men and 13–150 ng/mL for women.[14] All the methods' quality assurance

and quality control meet the Clinical Laboratory Improvement Act mandates.

Other covariates

Demographic data were collected from the interviews questionnaires. Biochemistry profiles include serum albumin, alanine aminotransferase, creatinine, and total bilirubin, which were measured on the Roche Cobas 6000 (c501 module) analyzer. Platelet counts were analyzed by the Beckman Coulter methodology of counting and sizing used to derive CBC counts. Body mass index is calculated as the ratio of an individual's weight in kilograms divided by the height in meters squared. Liver disease history was according to participants' medical records. Smoking status was based on the questions: "Smoked at least 100 cigarettes in life" and "Do you now smoke cigarettes?". Alcohol drinking status was defined as drink at least twice a week during the past 12 months.

Statistical analysis

We applied the Statistical Package for the Social Sciences (version 18.0, SPSS Inc., Chicago, IL, USA) for all data analysis. The ANOVA test was used for continuous data, and the Chi-square test was applied to categorize data. The participants were separated into four groups according to the quartile of serum iron concentration. Multivariable linear regression models were used to investigate the relationships between participant liver stiffness and serum iron biomarkers. Kolmogorov–Smirnov test was applied to check normality, and log-transformed LSM was applied to fix the nonnormal distribution. Receiving operating characteristic (ROC) curve analysis was applied to calculate the optimal cutoff points for serum iron concentration. The area under the ROC curve (AUROC) and the corresponding 95% confidence intervals (CIs) to determine the associations between serum iron and liver fibrosis. $P < 0.05$ indicated a statistically significant difference.

Table 1: Characteristics of the study participants

Characteristic	Quartile 1 (*n*=1376)	Quartile 2 (*n*=1378)	Quartile 3 (*n*=1392)	Quartile 4 (*n*=1366)	Total (*n*=5512)	*P*
Continuous variables*						
Age (years)	42.86 (20.68)	47.38 (20.75)	46.95 (20.75)	43.28 (20.75)	45.13 (20.83)	<0.001
BMI (kg/m^2)	30.56 (8.58)	29.49 (7.26)	28.52 (6.85)	27.08 (6.37)	28.91 (7.42)	<0.001
Iron frozen, serum (μg/dl)	45.69 (12.13)	72.28 (6.12)	93.61 (6.93)	135.67 (29.81)	86.74 (36.83)	<0.001
TIBC (μg/dL)	338.93 (62.80)	319.58 (49.36)	324.06 (46.34)	328.94 (45.77)	327.87 (52.02)	<0.001
Ferritin (ng/mL)	91.91 (145.65)	139.45 (153.06)	158.70 (159.35)	185.11 (244.42)	143.78 (183.12)	<0.001
LSM (kPa)	6.14 (5.77)	5.93 (5.09)	5.86 (5.03)	5.72 (4.70)	5.91 (5.16)	0.182
Platelet count (1000 cells/uL)	266.50 (72.61)	243.67 (59.54)	239.97 (58.76)	236.39 (58.10)	246.63 (63.61)	<0.001
Albumin (μg/mL)	3.96 (0.34)	4.09 (0.33)	4.13 (0.31)	4.19 (0.31)	4.09 (0.33)	<0.001
ALT (IU/L)	18.38 (12.97)	21.15 (15.70)	22.34 (16.17)	24.56 (21.79)	21.60 (17.09)	<0.001
Creatinine (mg/dl)	0.85 (0.50)	0.90 (0.49)	0.88 (0.47)	0.87 (0.25)	0.87 (0.44)	0.020
Total bilirubin (mg/dL)	0.33 (0.18)	0.41 (0.24)	0.48 (0.25)	0.63 (0.34)	0.46 (0.28)	<0.001
Categorical variables†						
Gender, *n* (%)						
Male	450 (32.7)	678 (49.2)	740 (53.2)	857 (62.7)	2725 (49.4)	<0.001
Female	926 (67.3)	700 (50.8)	652 (46.8)	509 (37.3)	2787 (50.6)	
Race-ethnicity						
Mexican American	203 (14.8)	189 (13.7)	196 (14.1)	229 (16.8)	817 (14.8)	<0.001
Other Hispanic	113 (8.2)	132 (9.6)	133 (9.6)	136 (10.0)	514 (9.3)	
Non-Hispanic white	418 (30.4)	465 (33.7)	497 (35.7)	495 (36.2)	1875 (34.0)	
Non-Hispanic black	379 (27.5)	351 (25.5)	275 (19.8)	216 (15.8)	1221 (22.2)	
Other race - including multi-racial	263 (19.1)	241 (17.5)	291 (20.9)	290 (21.2)	1085 (19.7)	
Liver condition	47 (4.2)	62 (5.3)	71 (6.0)	72 (6.5)	252 (5.5)	0.133
Smoking	437 (37.4)	504 (41.2)	486 (39.8)	522 (44.3)	1949 (40.7)	0.007
Alcohol drinking	689 (73.4)	793 (76.7)	792 (77)	848 (81.7)	3122 (77.3)	<0.001

*Continuous variables are presented as mean (SD); †Categorical variables are presented as number (percentage). TIBC=Total iron-binding capacity; ALT=Alanine aminotransferase; LSM=Liver stiffness measurement; SD=Standard deviation; BMI=Body mass index

RESULTS

Demographics of the study participants

The characteristics of the study participants are presented in Table 1. A total of 5512 adults participated in this study, with mean age (standard deviation [SD]) 45.13 (20.83) years, 2725 (49.4%) were men and 2787 (50.6%) were women. The mean concentration (SD) of serum iron was 86.74 (36.83) μg/dl. Moreover, the quartile-based subgroups were divided by the serum iron concentration. The mean concentration (SD) of serum iron in Q1, Q2, Q3, and Q4 was 45.69 (12.13), 72.28 (6.12), 93.61 (6.93), and 135.67 (29.81) μg/dl, respectively. The mean concentration (SD) of total iron-binding capacity (TIBC) was 327.87 (52.02) μg/dL. The mean concentration (SD) of LSM of Q1, Q2, Q3, and Q4 was 6.14 (5.77), 5.93 (5.09), 5.86 (5.03), and 5.72 (4.70) μg/dl, respectively. Among total participants, 252 (5.5%) participants had liver conditions told to previous medical history, and 3122 (77.3) had habits of alcohol drinking which is defined as drinking any type of alcoholic beverage at least twice weekly in past years.

Correlations between body iron biomarkers and liver stiffness measurements

The relationship between serum iron concentration and LSM is demonstrated in Table 2. Linear regression analysis showed increasing serum iron concentration with decreasing LSM (β coefficient: –0.001; 95% CI: –0.001, –0.0001; P = 0.008) in an unadjusted model. Notably, the results are significant in the fully adjusted model (β coefficient: –0.0005; 95% CI: –0.001, –0.00008; P = 0.020). There is no significant correlation between TIBC and LSM. In contrast, serum ferritin concentration was positively correlated with LSM in fully adjusted model (β coefficient: 0.0002; 95% CI: –0.00006, 0.001; P = 0.121). Table 3 demonstrates the gender-specific association between serum iron and liver stiffness, and the no significant association in both men and women subgroups in the adjusted model. Table 4 demonstrates age-specific analysis. Significant negative association was noted in the younger group (age < 65 year) in adjusted model (β coefficient: –0.001; 95% CI: –0.001, –0.0002; P = 0.004). Table 5 demonstrates quartile-base analysis. Negative correlation with significance comparing the third and largest quartiles with the first quartile in a fully adjusted model. Quartile 4 had a more negative correlation between serum iron and LSM compared with quartile 1 with significance (β coefficient: –0.049; 95% CI: –0.087, –0.012; P = 0.001).

Table 2: Association between body iron parameters and liver stiffness measurement

Models	$B^{\dagger}$ (95% CI)	P
	Serum iron	
Model 1	−0.001 (−0.001-−0.0001)	0.008
Model 2	−0.001 (−0.001-−0.0005)	<0.001
Model 3	−0.001 (−0.001-−0.0001)	0.015
Model 4	−0.0005 (−0.001-−0.00008)	0.020
	TIBC	
Model 1	0.00001 (−0.0003-0.0003)	0.919
Model 2	0.0004 (0.00006-0.001)	0.021
Model 3	0.0002 (−0.00007-0.001)	0.139
Model 4	0.0002 (−0.00006-0.001)	0.121
	Ferritin	
Model 1	0.00004 (0.0004-0.001)	<0.001
Model 2	0.00004 (0.0003-0.0004)	<0.001
Model 3	0.00022 (0.00015-0.0003)	<0.001
Model 4	0.0002 (0.0002-0.0003)	<0.001

†β coefficient can be interpreted as differences in the mean stiffness. Adjusted covariates: Model 1=Unadjusted; Model 2=Age, gender, race; Model 3=Model 2+ (BMI, platelet count, albumin, ALT, creatinine, and total bilirubin); Model 4=Model 3 + (liver condition, smoking, and alcohol drinking). BMI=Body mass index; ALT=Alanine aminotransferase; TIBC=Total iron binding capacity; CI=Confidence interval

Associations between serum iron concentration and suspected liver fibrosis

There are four stages of liver fibrosis measured by Fibroscan, F0-F4. The cut-off value of F0-F4 was variable in different liver health condition. F ≥F2 was considered suspected liver fibrosis (which defined as LSM ≥8.2 kPa).[15] To determine the ability of serum iron to predict the occurrence of suspected liver fibrosis, the optimal cutoff points for serum iron in predicting occurrences LSM ≥8.2 kPa was calculated using ROC analysis. Accordingly, in predicting occurrence of LSM ≥8.2 kPa, serum iron concentration had an AUROC of 0.539 (95% CI: 0.512–0.565; P = 0.004) with an optimal cutoff point of 88.50 determined by maximal Youden's index (sensitivity: 46.2%; specificity: 61.7%) [Figure 1].

DISCUSSION

The most prominent findings of this study performed indicate that serum iron concentration is negatively correlated with liver stiffness. In subgroup analysis, the inverse correlations were disclosed in groups adults under 65. Among iron biomarkers, there is no statistical association between TIBC and liver stiffness. Moreover, the results also indicated that the highest quartile of serum iron had more significantly negative correlation with LSM compared with the lowest quartile. Contrarily, liver stiffness is positively correlated with ferritin in a fully adjusted model.

Liver stiffness is a novel parameter for the diagnosis of liver fibrosis.[16] Excess iron activates hepatocytes, and Kupffer

Table 3: Gender-specific association between serum iron concentration and liver stiffness measurement

Models	Men		Women	
	β‡ (95% CI)	*P*	β‡ (95% CI)	*P*
Model 1	−0.001 (−0.002-−0.0004)	<0.001	−0.001 (−0.001-−0.0002)	0.010
Model 2	−0.001 (−0.001-−0.0003)	0.002	−0.001 (−0.001-−0.0002)	0.005
Model 3	−0.001 (−0.012-0.00007)	0.086	−0.0005 (−0.001-0.00009)	0.097
Model 4	−0.0005 (−0.001-0.0001)	0.110	−0.0005 (−0.001-0.0001)	0.109

†β coefficient can be interpreted as differences in the mean stiffness. Adjusted covariates: Model 1=Unadjusted; Model 2=Age and race; Model 3=Model 2+ (BMI, platelet count, albumin, ALT, creatinine, and total bilirubin); Model 4=Model 3 + (liver condition, smoking, and alcohol drinking). BMI=Body mass index; ALT=Alanine aminotransferase; CI=Confidence interval

Table 4: Age-specific association between serum iron concentration and liver stiffness measurement

Models	Young (<65-year-old)		Old (≥65-year-old)	
	β‡ (95% CI)	*P*	β‡ (95% CI)	*P*
Model 1	−0.001 (−0.001-−0.0003)	0.002	0.0003 (−0.001-0.001)	0.577
Model 2	−0.001 (−0.002-−0.001)	<0.001	0.0001 (−0.001-0.001)	0.814
Model 3	−0.001 (−0.001-−0.002)	0.003	0.0002 (−0.001-0.001)	0.661
Model 4	−0.001 (−0.001-−0.0002)	0.004	0.0003 (−0.001-0.001)	0.598

†β coefficient can be interpreted as differences in the mean stiffness. Adjusted covariates: Model 1=Unadjusted; Model 2=Age, gender, race; Model 3=Model 2+ (BMI, platelet count, albumin, ALT, creatinine, and total bilirubin); Model 4=Model 3 + (liver condition, smoking, and alcohol drinking). BMI=Body mass index; ALT=Alanine aminotransferase; CI=Confidence interval

cells and release the pro-inflammatory and profibrogenic cytokines. In the hepatocyte, iron is one of the key elements that activate oxidative stress. Iron can generate toxic reactive oxygen species (ROS) through the Fenton reaction. In a series of activation of the cells and pro-inflammatory process, transforming Growth Factor Beta (TGF-β) increases and activates HSCs to produce excess ECM such as pro-collagen-1 α-1, alpha-smooth muscle actin, fibronectin, etc., and initiate the process of the liver fibrogenesis.[17] In iron overload, or hemochromatosis patients, liver iron concentration correlates with the risk of liver fibrosis and cirrhosis.[18] In our study, iron levels were obtained from serum samples rather than liver samples, which found opposite results.

The liver is one of the major storage organs of body iron, a decrease in serum iron would reduce the iron storage in the liver and the labile iron, which is considered to reduce the activation of HSCs and progression and liver fibrogenesis. There are several possible reasons for the opposite results. Normal liver iron concentration is <35 μmol/g. HCS functionality begins to derail when liver iron concentration crosses a threshold of 60 μmol/g. This study enrolled participants in generally healthy adults, and the mean concentration of serum iron was measured within normal ranges. Serum iron is dynamic *in vivo*, while the labile iron is <0.2% of total iron.[3] The liver iron concentration would not easily cross the threshold under

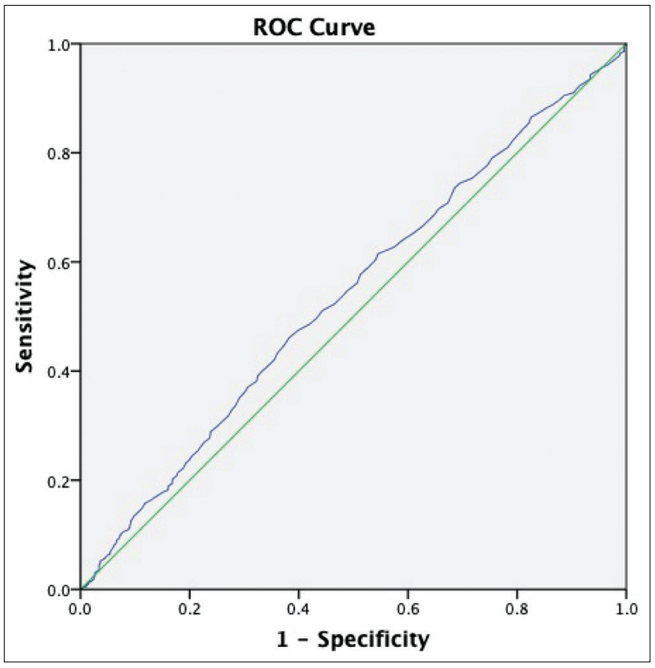

Figure 1: Receiver operating characteristic curve analysis for optimal cutoff points of serum iron in predicting occurance of LSM ≥8.2 kPa. LSM: Liver stiffness measurement

normal physiological status. In normal circumferences, iron is tightly controlled to promote cell growth and protect the cell against toxicity. ROS itself has both beneficial and harmful effects. Advantageously, ROS act as signaling molecules and trigger cell survival, differentiation, or cell death according to the needs of the cell or organism. Disadvantageously, ROS can damage biomolecules and cause cellular mutations and other cellular dysfunctions.[19]

The study figured that, in the younger group, serum iron concentration is a significant inverse association with liver stiffness. A previous study indicated that in children without evidence of liver disease, LSM has an age-dependent increase.[20] While in the adult population, there were no statistically significant differences between the mean values of liver stiffness in various age subgroups.[21] Iron deficiency is prevalent in older age. Serum iron and ferritin concentrations

Table 5: Quartile-based association between serum iron concentration and liver stiffness measurement

Models	$B^{\dagger}$ (95% CI)	*P*
Model 1		
Q2 versus Q1	−0.012 (−0.053-0.029)	0.557
Q3 versus Q1	−0.046 (−0.087-−0.005)	0.026
Q4 versus Q1	−0.052 (−0.094-−0.011)	0.013
Model 2		
Q2 versus Q1	−0.040 (−0.080-0.001)	0.054
Q3 versus Q1	−0.073 (−0.113-0.033)	<0.001
Q4 versus Q1	−0.092 (−0.133-−0.051)	<0.001
Model 3		
Q2 versus Q1	−0.018 (−0.056-0.019)	0.332
Q3 versus Q1	−0.052 (−0.089-−0.014)	0.007
Q4 versus Q1	−0.055 (−0.095-−0.015)	0.008
Model 4		
Q2 versus Q1	−0.017 (−0.054-0.021)	0.381
Q3 versus Q1	−0.049 (−0.087-−0.012)	0.010
Q4 versus Q1	−0.053 (−0.093-−0.012)	0.011

†β coefficient can be interpreted as differences in the mean stiffness. Adjusted covariates: Model 1=Unadjusted; Model 2=Age, gender, race; Model 3=Model 2+ (BMI, platelet count, albumin, ALT, creatinine, and total bilirubin); Model 4=Model 3 + (liver condition, smoking, and alcohol drinking). BMI=Body mass index; ALT=Alanine aminotransferase; CI=Confidence interval

also decline. Hepatocyte structure changes with age. In animal models, age-related changes in liver function are the demonstration of a significant decrease in the regenerative capacity of the liver. A previous study demonstrated that age at viral infection was a major risk factor for subsequent fibrosis progression and further, that the rate of fibrosis progression accelerated with increasing age.[22] Chronic inflammation is a common condition in older people, making the measurement of iron status difficult, and elevated levels of circulating hepcidin are likely responsible for changes in iron metabolism that result in systemic iron depletion.[23] We analyze gender-specific subgroup analysis. Women tended to have smaller total body iron storage than men due to smaller body size, lower androgen levels, and chronic iron loss through menses, pregnancy, and lactation. Iron deficiency occurs due to regular iron losses, increased requirements, or decreased intake. In premenopausal women, cumulative menstrual blood loss is a common cause of the iron deficiency. In this study, we figured no significant association between serum iron and LSM in both gender subgroups.

Iron deficiency is considered associated with multiple chronic diseases. Iron is essential for forming mitochondrial respiratory chain complexes, and iron deficiency leads to an overall impairment of mitochondrial respiration, which is crucial for fatty acid metabolism. Regulation of iron homeostasis is mainly through iron regulatory proteins/iron-responsive elements and hepcidin. Serum iron is reduced in anemia of chronic disease, reflecting the decreased availability of iron. Lower iron levels increase oxidative stress in red blood cell.[24] Previous studies investigated that serum iron was inversely associated with the incidence of cardiovascular disease and diabetic retinopathy.[25,26] Deficiency of serum iron leads to greater susceptibility to lipid accumulation in hepatocytes, which is associated with increased liver fibrosis.[27] Ferritin and hemosiderin reflect the iron storage. Serum ferritin is the most convenient laboratory test to estimate iron stores. The body would store iron in ferritin form when serum iron overload, or reducing iron demand. Serum ferritin is also a common inflammatory marker, but it is unclear whether serum ferritin reflects or causes inflammation, or whether it is involved in an inflammatory cycle. In NAFLD, elevated serum ferritin is not only an independent predictor of advanced fibrosis but also correlates with disease severity. The decreased levels of hepcidin in cirrhotic patients have been found to cause hepatic iron accumulation and may also contribute to the progression of liver fibrosis.[28,29] It is also possible that the proposed relation between iron stores and an inflammatory response is reversely causal, which means inflammation affects body iron stores. Inflammation has been associated with increased serum ferritin as well as decreased serum iron and transferrin saturation.[30] In the quartile-based analysis, we discovered a negative correlation in the highest quartiles of serum iron concentration with liver stiffness in a fully adjusted model compared to the lowest quartile. Even though the mean value of serum iron of the participants is within the normal range, this result supports the idea of relatively higher serum iron concentration had better balanced body serum iron homeostasis and better hepcidin function, less pro-inflammatory state of liver health.

The study has several limitations. First, this was a cross-sectional study, we cannot infer causality from these associations in a single period. Second, the evaluation of anemia and hemoglobin is limited. Body iron was stored in hemoglobin. In different circumstances, the homeostasis of body iron was adjusted by several cytokines and enzymes. The hemoglobin level and anemic status may be helpful for the evaluation of total body iron content; however, in the evaluation of chronic disease or pro-inflammatory status, serum iron would be more proper due to the ion activity and the physiological function. Third, the information of diet supplements of iron in the participants is limited. Forth, liver stiffness measured by transient elastography has some limitations and false-positive conditions. Chronic liver health evaluation required longitudinal assessment that corresponds to histologic changes in fibrosis.

CONCLUSION

This study highlights the inverse association between serum iron concentrations and liver stiffness in the general healthy population, especially in nongeriatric adults. Elevated serum ferritin is significantly associated with liver stiffness. Liver stiffness is a novel way to screen liver health, increasing liver stiffness is a possible inflammation process in the liver. These findings underscore that, within the general population, especially nongeriatric adults, body serum homeostasis is associated with liver health. Decrease serum iron or increase ferritin implies the possible pro-inflammatory process of the liver, and within the normal range, higher serum iron level and lower serum ferritin are considered to be a balance status of body iron homeostasis and reduced the risks of liver fibrosis.

Data availability statement

The datasets generated and/or analyzed during the current study are available in the National Health and Nutrition Examination Survey. (https://www.cdc.gov/nchs/nhanes/index.htm)

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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