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Serum cadmium is associated with hepatic steatosis and fibrosis

Korean national health and nutrition examination survey data IV–VII

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Abstract

Although cadmium (Cd) is correlated with elevated levels of hepatic amino transferases, its influence on the degree of liver steatosis and fibrosis are unknown yet. We aimed to investigate the associations between the serum level of Cd and degree of liver steatosis/fibrosis.

Clinical data were obtained from Korean National Health and Nutrition Examination Surveys IV–VII. Alanine aminotransferase (ALT) elevation was defined as ≥ 33 IU/L for men and ≥ 25 IU/L for women. Significant steatosis was defined as a hepatic steatosis index ≥ 36, while significant fibrosis was defined as a fibrosis index (FIB-4) ≥ 2.67 and as an aspartate aminotransferase and platelet ratio index ≥ 0.7. Adjusted odds ratios and 95% confidence intervals were calculated after adjustment.

The levels of serum Cd were assessable in 15,783 subjects. The serum cadmium concentrations were significantly associated with ALT elevation, significant liver steatosis and fibrosis. Multivariate logistic regression analysis demonstrated serum Cd level in the forth quartile had a positive correlation with ALT elevation, hepatic steatosis index ≥ 36, FIB-4 ≥ 2.67 and aspartate aminotransferase-to-platelet ratio ≥ 0.7 using the first quartile of serum Cd level as the reference, (adjusted odds ratios 1.90, 1.26, 1.73, and 2.53, respectively; *P* values <.001).

The serum level of Cd was associated with liver steatosis and fibrosis. The evaluation of serum Cd may help for assessing an unexplained liver steatosis and fibrosis, and further prospective studies are needed to confirm our findings.

Abbreviations: ALT = alanine aminotransferase, AORs = adjusted odds ratios, APRI = AST-to-platelet ratio, AST = aspartate aminotransferase, BMI = body mass index, Cd = cadmium, CIs = confidence intervals, DM = diabetes mellitus, HSI = hepatic steatosis index, HT = hypertension, KNHANES = Korea National Health and Nutrition Examination Surveys.

Keywords: cadmium, cirrhosis, hepatic fibrosis, hepatic steatosis

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Sangheun Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Sangheun Lee and Ki Jun Han were responsible for study concept and design. Hyun-Jeong Han conducted the research; Gi-Ho Sung and Seogoo Han analyzed the data and wrote the manuscript. All authors read and approved the final manuscript. Sangheun Lee is a guarantor. All authors reviewed the manuscript.

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Highlight

- Serum cadmium is correlated with elevated levels of hepatic amino transferases and the degree of liver steatosis.
- Serum cadmium is also associated with liver **fibrosis** regardless with obesity, diabetes mellitus or hypertension.
- The evaluation of serum cadmium can be considered for assessing an unexplained liver steatosis and fibrosis.

1. Introduction

Hepatic steatosis is a condition where excess fat builds up in the liver while hepatic fibrosis is the excessive accumulation of extracellular matrix proteins including fibrillar collagens. They occur in most types of chronic liver diseases.[1] The onset of liver steatosis and fibrosis is usually insidious, and most of the related morbidity and mortality occur after the development of cirrhosis.[2]

The main causes to liver fibrosis and cirrhosis are chronic viral diseases, alcohol abuse, fatty liver, and medications. Wilson disease, autoimmune hepatitis, and primary biliary cirrhosis are not common but can cause liver fibrosis and cirrhosis.[3] Several drugs (e.g., amiodarone, tamoxifen, antiretroviral nucleoside analogues) and environmental factors (e.g., industrial solvents) may be responsible for hepatic steatosis and fibrosis in chronic liver disease.[4,5]

Cadmium (Cd) is a well-known persistent environmental pollutant.[6] Cd exposure in the population was associated with osteoporosis, renal dysfunction, diabetes, cancer, blood pressure and reproduction.[7] Cd is also deposited in the liver for a long time, resulting in liver injury.[8,9] The studies in animal models have reported that exposure to Cd can cause acute and chronic hepatitis.[10,11] Chronic Cd exposure can lead oxidative stress by an imbalance in the cellular redox status.[12] Moreover, by depleting glutathione and other sulfhydryl groups, it aggravates the oxidative stress and cellular damage resulting in apoptosis.[13] After acute Cd exposure, the damaged liver is often infiltrated by polymorphonuclear neutrophils and Küpffer cells, which contribute to hepatotoxicity by releasing inflammatory mediators.[14] These initiate a cascade of cellular and humoral responses leading to inflammation and subsequently enhance promoting necrosis.[15]

There is a study in human that support this point. Kang et al reported the possibility of liver injury by Cd. In that study, the concentration of Cd in the serum was correlated with the elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[16] Even though the presence of advanced liver steatosis or fibrosis is the stronger determinant of liver-related mortality than simply elevated levels of liver enzymes, no one has studied that the association between serum Cd and hepatic steatosis/fibrosis. Therefore, here we aimed to investigate the possible link of serum Cd level with hepatic steatosis and fibrosis in the general population by using the database from the Korea National Health and Nutrition Examination Survey (KNHANES), a nationwide cross-sectional cohort with a nationally representative sample of the Korean population conducted annually by the Korea Centre for Disease Control and Prevention to regularly assess the health and nutritional status of general civilians.

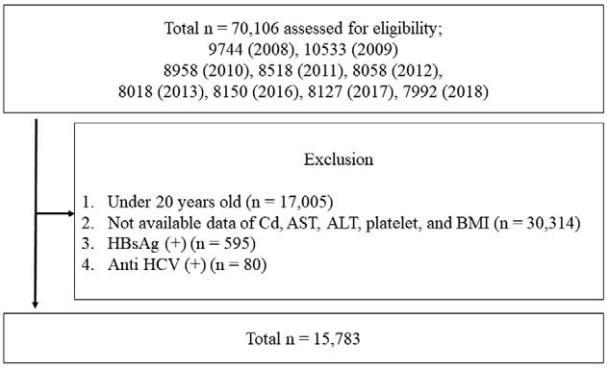

Figure 1. Study design.

2. Methods

2.1. Subjects eligibility

KNHANES is a nationwide cross-sectional investigation into the health behavior of citizens, prevalence rates of chronic diseases, food intake, and nutrition consumption status of a representative population in Korea. The survey was conducted by the Korea Centers for Disease Control and Prevention. This study was based on data acquired from the KNHANES IV–VII (2008–2013 and 2016–2017).

The study covered here included 18,859 people surveyed for the serum level of Cd among the subjects (n = 70,106) who undertook the 2008–2017 KNHANES. In all, 15,783 subjects were finally analyzed whose AST, ALT, platelet, and body mass index (BMI) data were available for noninvasive predictive models of hepatic steatosis and fibrosis. Subjects younger than 20 years of age were excluded from the analysis. Those with a positive hepatitis B surface antigen or anti hepatitis C virus antibody were excluded (Fig. 1). This study was approved by the institutional Review Board of Catholic Kwandong University, International St. Mary's Hospital (approval no. IS18EISI0050).

2.2. Measurements

In the KNHANES for these years, subjects were selected randomly for measurement of serum Cd level by gender and age. Serum Cd level were measured by atomic absorption spectrophotometry using a PerkinElmer AAnalyst 600 (PerkinElmer, Turku, Finland). Diabetes Mellitus (DM) was defined as a fasting blood glucose level ≥126 mg/dL, or when this disease had been diagnosed by a physician and the subject had been prescribed a hypoglycemic agent. Hypertension (HT) was defined as having a systolic blood pressure >140 mm Hg or a diastolic blood pressure > 90 mm Hg, or when the subject was taking an antihypertensive drug. Smoking status was categorized by self-reporting as never, ex-, or current smoker. The significant alcohol consumption was defined as >210 in g ethanol/wk for men and >140 in g ethanol/wk for women.[17]

2.3. Definition of liver steatosis and fibrosis

FIB-4 and the AST-to-platelet ratio (APRI) were selected to assess the severity of liver fibrosis. The FIB-4 and APRI indexes are the most commonly used formulae for predicting liver fibrosis as a combination of items capable of acquiring information from

blood tests.[18] The severity of fatty liver was expressed by hepatic steatosis index (HSI).[19] FIB-4 was calculated as age × AST (U/L)/platelet count (× 10^9/L) × √ALT (U/L).[20] APRI was calculated as AST (U/L)/(upper limit of normal AST (U/L))/platelet count × 10^9/L) × 100.[21] HSI was calculated as 8 × AST/ALT + BMI + (2 for women) + (2 if diabetes mellitus was present). ALT elevation was defined as ≥ 33 IU/L for men and ≥ 25 IU/L for women; significant steatosis as HSI ≥ 36, and significant fibrosis as FIB-4 ≥ 2.67 and APRI ≥ 0.7.[18,22]

2.4. Statistical analysis

The characteristics of the study subjects were analyzed using Student *t*-tests for continuous variables and $\chi 2$ tests for categorical variables. Continuous and categorical variables were expressed as the mean ± standard deviation (SD) and n (%), respectively. The association between serum Cd and liver steatosis and fibrosis prediction scores (HSI, APRI, and FIB-4) was evaluated using a $\chi 2$ test after transformation of these variables into quartiles. Multivariable logistic regression analysis was applied to determine the independent association between serum Cd and liver steatosis/fibrosis. Adjusted odds ratios (AORs) and confidence intervals using generalized estimating equations were calculated after adjusting for age, gender, residence area, economic status, BMI, HT, DM, smoking, and Significant alcohol consumption. To control for the effects of obesity or metabolic underlying disease, the study population was stratified into two groups depending on the presence of obesity (BMI≥25 kg/m^2), DM or HT. A P value $< .05$ was considered to be statistically significant. The analyses have been performed using the *R* statistics program (version 4.0.3).

3. Results

3.1. Subject characteristics

We investigated 15,783 subjects who were checked for serum Cd level using data derived from KNHANES IV–VII (2008–2013 and 2016–2017). The mean age of this study population was 46 years, and there were 8,210 (52.0%) women. The geometrical mean of the serum cadmium level was 1.105 ± 0.6 (μg/dL). Of all subjects, 12,799 (81.1%) were living in urban areas, 4,290 (27.6%) had HT and 1,480 (9.7%) had DM. Other baseline characteristics are listed in Table 1.

The incidence of unexplained ALT elevation (≥ 33 IU/L for men and ≥ 25 IU/L for women) was 2625 (16.6%), and significant steatosis (HSI ≥ 36) was 3630 (22.9%). The prevalence of significant liver fibrosis with FIB-4 ≥ 2.67 and APRI ≥ 0.7 were 265 (1.6%) and 201 (1.2%), respectively.

The serum Cd were divided into quartiles (Q1, Q2, Q3, Q4) for analysis. For Cd (μg/dL), Q1 was < 0.651, Q2 was 0.651–0.973, Q3 0.973–1.413 and Q4 was ≥ 1.413.

Table 1

Demographic and clinical characteristics (total n = 15,783).

Variables	Values
Age (yr)	46 ± 15
Gender (female)	8210 (52.0%)
Region	
Urban	12,799 (81.1%)
Rural	2984 (18.9%)
Economic status	
Low	2535 (16.0%)
Mid Low	4044 (25.6%)
Mid High	4419 (28.0%)
High	4635 (29.4%)
Missing	150 (1.0%)
Education	
Elementary school	2818 (17.9%)
Middle school	1595 (10.1%)
High school	5532 (35.1%)
College	5366 (34.0%)
Missing	472 (2.9%)
Hypertension*	4290 (27.6%)
Diabetes†	1480 (9.7%)
Smoking	
Current	8699 (55.1%)
Past	2422 (15.3%)
Never	4368 (27.7%)
Missing	294 (1.9%)
Significant alcohol consumption‡	866 (5.6%)
Fasting glucose (mg/dl)	98.5 ± 22.9
Total cholesterol (mg/dl)	189.7 ± 36.9
HDL cholesterol (mg/dl)	49.9 ± 12.1
LDL cholesterol (mg/dl)	114.1 ± 33.0
Triglycerides (mg/dl)	137.7 ± 116.1
Cadmium (μg/dL)	1.105 ± 0.6
AST (IU/L)	22.2 ± 14.3
ALT (IU/L)	21.9 ± 16.7
Blood Urea Nitrogen (mg/dl)	14.1 ± 4.3
Creatinine (mg/dl)	0.8 ± 0.3

ALT = alanine aminotraferase, AST = aspartate aminotransferase, HDL = High - density lipoprotein, LDL = Low – density lipoprotein, sd = standard deviation.

* Hypertension was defined as having a systolic blood pressure >140 mm Hg or a diastolic blood pressure > 90 mm Hg, or when the subject was taking an antihypertensive drug.

† Diabetes was defined as a fasting blood glucose level ≥126 mg/dL, or when this disease had been diagnosed by a physician and the subject had been prescribed a hypoglycemic agent.

‡ Significant alcohol consumption was defined as >210 in g ethanol/week for men and 140 in g ethanol/week for women.

3.2. Independent association between serum Cd and ALT elevation by quartiles stratification

Table 2 summarizes the results of the linear regression model exploring the association of blood Cd quartiles with ALT elevation. Using the first quartile of serum Cd as the reference, the AORs (confidence intervals) of second, third and fourth quartiles were 1.31 (1.14–1.49), 1.45 (1.26–1.66) and 1.90 (1.65–2.19), respectively ($P < .001$). The mean serum level of Cd in subjects with ALT elevation was higher than in those with normal ALT [1.21 (±0.7) versus 1.09 (±0.6), respectively; $P < .001$].

3.3. Independent association between serum Cd and steatosis burden (HSI≥36) by quartiles stratification

The prevalence of HSI quartiles gradually increased with increasing Cd quartiles (P for trend $< .001$; Fig. 2A). Using the first quartile of blood Cd level as the reference, blood Cd level in the second, third and fourth quartiles had a positive correlation with a high HSI (≥ 36) [AOR (CI); 1.13 (1.01–1.27), 1.17 (1.03–1.32), 1.26 (1.11–1.43); Table 2]. The mean serum level of Cd in subjects with a high HSI (≥ 36) was higher than in those with a low HSI (< 36) [1.14 (±0.6) versus 1.10 (±0.6), respectively; $P = .002$].

Table 2

Adjusted odds ratios with 95% confidence intervals of alanine aminotransferase elevation, hepatic steatosis index, FIB-4 and aspartate aminotrasnferase to platelet ratio index by age, gender, body mass index, hypertension, diabetes mellitus, smoking, and alcohol consumption.

Concentration	ALT elevation	HSI (≥ 36)	APRI (≥ 0.7)	FIB-4 (≥ 2.67)
Cd (μg/dL)				
< 0.651	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
0.651–0.973	1.31 (1.14–1.49)***	1.13 (1.01–1.27)*	1.05 (0.64–1.73)	1.07 (0.64–1.82)
0.973–1.413	1.45 (1.26–1.66)***	1.17 (1.03–1.32)*	1.25 (0.77–2.07)	1.28 (0.81–2.14)
≥ 1.413	1.90 (1.65–2.19)***	1.26 (1.11–1.43)***	2.53 (1.61–4.07)***	1.73 (1.09–2.87)*

ALT = alanine aminotransferase, APRI = aspartate aminotrasnferase to platelet ratio index, CI = Confidence Interval, HSI = hepatic steatosis index, OR = Odds ratio.

The model was adjusted for age (continuous), gender, residence area, economic status, body mass index (continuous), diabets, hypertension, smoking and alcohol consumption (g/wk)

* Denotes statistical significance at $P < .05$.

** denotes statistical significance $P < .01$.

*** denotes statistical significance $P < .001$.

3.4. Independent association between serum Cd and significant liver fibrosis (FIB-4 ≥ 2.67 and APRI ≥ 0.7) by quartiles stratification

The prevalence of FIB-4 and APRI quartiles gradually and markedly increased with increasing Cd quartiles (P for trend $<.001$) (Fig. 2B and 2C). The Cd levels showed a strong positive relationship with FIB-4 [AOR was 1.73 (1.09–2.87) of the forth quartile compared with the first quartile; Table 2]. We observed similar results when we compared the blood Cd levels with a high APRI (≥ 0.7) [AOR was 2.53 (1.61–4.07) of the forth quartile compared with the first quartile; $P < .001$; Table 2]. Subjects with a high FIB-4 (≥2.67) showed a significant elevation in mean serum Cd levels compared with those with a low FIB-4 (<2.67] [1.42 (±0.6) versus 1.10 (±0.7) μg/dL, respectively; $P < .001$]. Subjects with a high APRI (≥ 0.7) also showed significant elevations in mean serum Cd levels compared with those with a low APRI (< 0.7) [1.39 (±0.8) versus 1.10 (±0.6) μg/dL, respectively; $P < .001$].

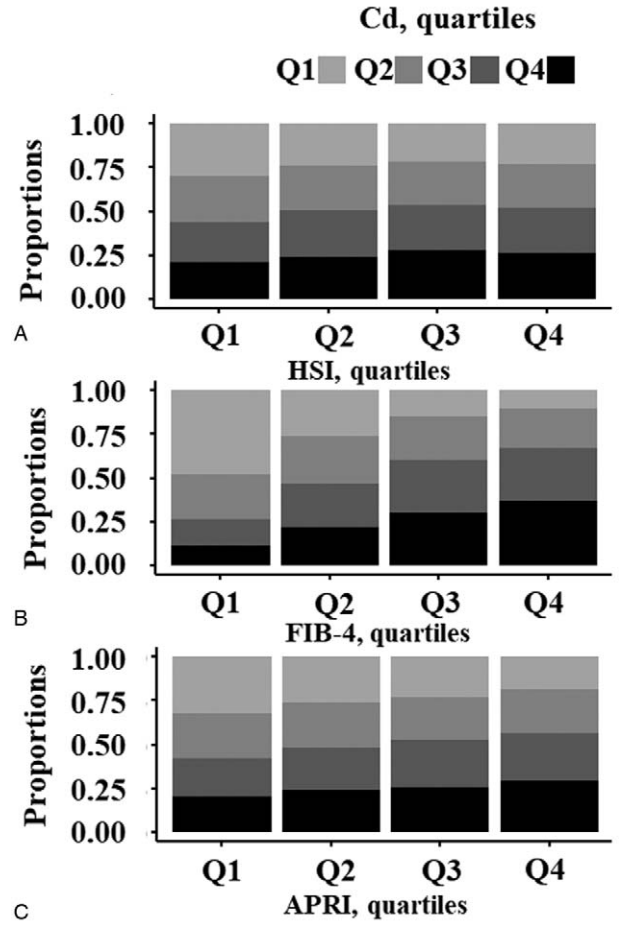

Figure 2. Correlations between HSI (A), FIB-4 (B), APRI (C) and the serum level of cadmium (Cd) by quartile stratification analysis. The serum level of Cd showed strong positive relationships with HSI, FIB-4, and APRI (all $Ps < .001$).

3.5. Degree of liver fibrosis and serum Cd stratified by DM, HT and BMI

We further investigated the association between serum Cd and the degree of liver steatosis and fibrosis by stratifying the study population using DM, HT, and BMI. When we calculated significant liver fibrosis using APRI and FIB-4, we found a significant higher level of serum Cd in subjects with liver steatosis and fibrosis than subjects without. The subjects with high FIB-4 (FIB-4 ≥2.67) had a significantly higher serum Cd than subjects with low FIB-4 (FIB-4 <2.67) regardless of DM [mean serum Cd1.47 ± 0.6 (μg/dL) vs 1.23 ± 0.7 (μg/dL) in subjects with DM and 1.41 ± 0.7 (μg/dL) vs 1.09 (±0.6) (μg/dL) in subjects without DM (all $Ps < .001$)]. When we used APRI to assess liver fibrosis, we obtained comparable results (Table 3). Similar results were obtained when the subjects were divided by hypertension and BMI, showing a higher serum cadmium level in the subjects with fibrosis or steatosis than in the subjects without (Tables 4 and 5).

4. Discussion

Chronic hepatitis can progress to liver fibrosis and cirrhosis.[23–25] To prevent this progression, it is important to identify the cause of the disease and to correct the causal factors.[26–28] Although more studies are still needed, antifibrotic drug such as lactoferrin was suggested for the treatment of liver fibrosis.[29]

However, we sometimes have cases where it is difficult to determine the cause of cirrhosis even after excluding viral hepatitis, nonalcoholic fatty liver disease, alcoholic hepatitis, and genetic liver disorders.[30] Therefore, some challenging trials are required to find new potential causes.

Most of the heavy metals emit into the atmosphere and are ultimately absorbed into the human body through the

Table 3

The mean differences of serum Cd (μg/dL) according to alanine aminotranferase elevation, Hepatic Steatosis Index, Aspartate aminotrasnferase to platelet ratio index and FIB-4 stratified by diabetes mellitus.

Without DM			With DM		
normal ALT, n=12,102	elevated ALT, n=2,201	*P* value	normal ALT, n=1056	elevated ALT, n=424	*P* value
1.07±0.6	1.19±0.7	<.001	1.22±0.6	1.29±0.8	.356
HSI (<36), n=11,464	HSI (≥36), n=2,839	*P* value	HSI (<36), n=689	HSI (≥36), n=791	*P* value
1.09±0.6	1.12±0.6	.101	1.25±0.6	1.22±0.7	.09
APRI (< 0.7), n=14,144	APRI (≥ 0.7), n=159	*P* value	APRI (< 0.7), n=1438	APRI (≥ 0.7), n=42	*P* value
1.09±0.6	1.37±0.9	<.001	1.23±0.7	1.44±0.7	.001
FIB-4 (< 2.67), n=14,102	FIB-4 (≥ 2.67), n=201	*P* value	FIB-4 (< 2.67), n=1416	FIB-4 (≥ 2.67), n=64	*P* value
1.09±0.6	1.41±0.7	<.001	1.23±0.7	1.47±0.6	<.001

ALT=alanine aminotransferase, APRI=aspartate aminotrasnferase to platelet ratio index, DM=diabetes mellitus, HSI=hepatic steatosis index.

atmosphere, water, soil, and food. Previous studies have reported that Cd can cause various systemic diseases,[31–33] and be highly correlated with elevated liver enzymes.[16] Here we also found that serum Cd level was positively correlated with elevated serum ALT level. In fact, previous studies concerning Cd and other heavy metals have defined liver dysfunction simply as elevated liver enzyme levels including AST, ALT, and gamma-glutamyltransferase.[16,34,35]

However, elevated levels of aminotransferase were poor surrogate marker for inflammation and fibrosis compared by histological variables.[36] Elevated levels of AST, ALT or Gamma-glutamyltransferase do not imply a hepatic dysfunction. Even though inflammation might be present in the liver, the value of bilirubin, albumin and prothrombin time can still be normal. The Child–Pugh classification and the Model for End-Stage Liver Disease score, which are used to evaluate liver function, do not reflect AST or ALT concentrations.[37,38] In addition, elevated levels of liver enzymes do not strongly reflect liver-related **prognosis** such as cirrhosis and liver cancer, or long-term overall survival.[39,40] Therefore, evaluating hepatic fibrosis in itself rather than simple elevations of AST or ALT seems to be more clinically relevant. From this perspective, our study is important because, to our knowledge, it is the first study between Cd exposure of human and liver steatosis/fibrosis in a large population-based sample. We evaluated the prevalence of hepatic steatosis and fibrosis using the noninvasive measurements HSI, FIB-4, and APRI. When the first quartile of the blood Cd was used as the reference, forth quartile of blood Cd levels showed

Table 4

The mean differences according to alanine aminotransferase elevation, hepatic steatosis index, aspartate aminotrasnferase to platelet ratio and FIB-4 stratified by hypertension.

Without HT			With HT		
normal ALT, n=8814	elevated ALT, n=1315	*P* value	normal ALT, n=4,344	elevated ALT, n=1,310	*P* value
1.00±0.5	1.11±0.6	<.001	1.25±0.6	1.30±0.7	<.001
HSI (<36), n=8364	HSI (≥36), n=1765	*P* value	HSI (<36), n=3,789	HSI (≥36), n=1,865	*P* value
1.01±0.5	1.05±0.6	.109	1.3±0.7	1.2±0.7	.003
APRI (< 0.7), n=10,052	APRI (≥ 0.7), n=77	*P* value	APRI (< 0.7), n=5,530	APRI (≥ 0.7), n=124	*P* value
1.01±0.6	1.22±0.7	.003	1.26±0.7	1.49±0.8	<.001
FIB-4 (< 2.67), n=10,030	FIB-4 (≥ 2.67), n=99	*P* value	FIB-4 (< 2.67), n=5,488	FIB-4 (≥ 2.67), n=166	*P* value
1.01±0.6	1.32±0.7	<.001	1.26±0.7	1.49±0.8	<.001

ALT=alanine aminotransferase, APRI=aspartate aminotrasnferase to platelet ratio index, HSI=hepatic steatosis index, HT=hypertension.

Table 5

The mean differences according to alanine aminotransferase elevation, Hepatic steatosis index, Aspartate aminotrasnferase to platelet ratio index and FIB-4 stratified by body mass index.

With low BMI			With high BMI		
normal ALT, n=9482	elevated ALT, n=1110	*P* value	normal ALT, n=3676	elevated ALT, n=1515	*P* value
1.07±0.6	1.24±0.7	<.001	1.12±0.6	1.18±0.7	.002
HSI (<36), n=10,079	HSI (≥36), n=513	*P* value	HSI (<36), n=2074	HSI (≥36), n=3117	*P* value
1.09±0.6	1.12±0.7	.739	1.09±0.6	1.12±0.7	.803
APRI (< 0.7), n=10,470	APRI (≥ 0.7), n=122	*P* value	APRI (< 0.7), n=5112	APRI (≥ 0.7), n=79	*P* value
1.09±0.6	1.52±0.9	<.001	1.13±0.6	1.20±0.6	.375
FIB-4 (< 2.67), n=10,393	FIB-4 (≥ 2.67), n=199	*P* value	FIB-4 (< 2.67), n=5125	FIB-4 (≥ 2.67), n=66	*P* value
1.08±0.6	1.47±0.7	<.001	1.13±0.7	1.28±0.6	.002

ALT=alanine aminotransferase, APRI=aspartate aminotrasnferase to platelet ratio index, BMI=body mass index, HSI=hepatic steatosis index.

significant correlations with steatosis (AOR 1.26 for HSI ≥ 36) and fibrosis (AOR 1.73 for FIB-4 ≥ 2.67, and AOR 2.53 for APRI ≥ 0.7) in our study using representative KNHANES data. Based on our results and the previous study for the association an increase in urinary Cd and an increase in liver – related mortality,[41] serum blood Cd level might also lead to an increase in the incidences of liver steatosis and fibrosis, which can affect mortality adversely. DM, HT and BMI are well known predictors for steatosis and fibrosis.[42–44] Interestingly, serum Cd levels were higher in subjects with significant steatosis and fibrosis than without significant steatosis and fibrosis regardless with obesity, DM or HT.

Based on this study, we think evaluating serum Cd concentration may be helpful in clinical practice. The United States Environmental Protection Agency suggested 1.7 μg/dL as a reference value for the serum Cd concentration in the general population. [45] In our study, more than 1.413 μg/dL of the serum Cd concentration is also strongly associated with ALT elevation, hepatic steatosis and hepatic fibrosis. To evaluate chronic exposure to cadmium may be considered when the cause of fatty liver or liver fibrosis is not clear. In addition, chronic exposure to cadmium may be expected to affect the prognosis of patients with liver disease as well as diabetes, hypertension, and obesity.

Our study had some drawbacks. First, the gold standard for diagnosing liver steatosis and fibrosis is a liver biopsy. However, the information obained from liver biopsy was not included in the KNHANES data, so indirect and noninvasive tests for measuring liver fibrosis were used. HSI, FIB-4, and APRI are important noninvasive methods for assessing liver steatosis and fibrosis. They has been used in replace of liver biopsies in previous studies.[46] Second, in light of the cross-sectional nature of this study, we cannot infer any cause–effect relationships between the serum Cd level and liver steatosis/fibrosis. However, a large sample size was established to minimize sampling errors.

In conclusion, elevated serum Cd level was associated with liver steatosis and fibrosis in this KNHANES-based study. Cd needs to be confirmed as a possible cause of unexplained liver steatosis and fibrosis, and further prospective studies are needed to confirm our findings.

Author contributions

Conceptualization: Sangheun Lee.
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Funding acquisition: Sangheun Lee.
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Supervision: Sangheun Lee.
Validation: Seogoo Han.
Writing – original draft: Seogoo Han, Sangheun Lee, Ki Jun Han.
Writing – review & editing: Gi-Ho Sung, Sangheun Lee, Hyun-Jeong Han.

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