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
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. The onset of liver steatosis and fibrosis is usually insidious, and most of the related morbidity and mortality occur after the development of cirrhosis.

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 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. 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.

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

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). 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.

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 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.

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. The severity of fatty liver was expressed by hepatic steatosis index (HSI). FIB-4 was calculated as age × AST (U/L)/platelet count (× 10^9/L) × √ALT (U/L).

APRI was calculated as AST (U/L)/(upper limit of normal AST (U/L))/platelet count × 10^9/L) × 100. 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.

2.4. Statistical analysis

The characteristics of the study subjects were analyzed using Student t-tests for continuous variables and χ² 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 χ² 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/m²), 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 prevalence 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.

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 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    | 4200 (27.6%) |
| Diabetes        | 1490 (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 aminotransferase, 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 g ethanol/week for men and 140 g ethanol/week for women.
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].

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, anti-fibrotic 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 amionotransferase elevation, Hepatic Steatosis Index, Aspartate aminotransferase 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=1,056 | 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=1,438 | 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=1,416 | 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 aminotransferase to platelet ratio index, DM = diabetes mellitus, HSI = hepatic steatosis index.

Table 4

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

|                  | Without HT | With HT |
|------------------|------------|---------|
|                  | normal ALT, n=8,814 | elevated ALT, n=13,15 | 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=8,836 | HSI (≥36), n=1,765 | 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 aminotransferase to platelet ratio index, HSI = hepatic steatosis index, HT = hypertension.

Table 5

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

|                  | With low BMI | With high BMI |
|------------------|--------------|--------------|
|                  | normal ALT, n=9,482 | elevated ALT, n=1,110 | P value | normal ALT, n=3,676 | elevated ALT, n=1,515 | 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=2,074 | HSI (≥36), n=3,117 | 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=5,112 | 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=5,125 | 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 aminotransferase to platelet ratio index, BMI = body mass index, HSI = hepatic steatosis index.
significant correlations with steatosis (AOR 1.26 for \( HSI \geq 36 \)) and fibrosis (AOR 1.73 for \( \text{FIB-4} \geq 2.67 \), and AOR 2.53 for \( \text{APRI} \geq 0.7 \)) 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, 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 \( \mu \text{g/dl} \) as a reference value for the serum Cd concentration in the general population.\(^{45}\) In our study, more than 1.413 \( \mu \text{g/dl} \) 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 obtained 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 have 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**

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