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Changes in zinc and manganese concentrations in cisplatin-induced acute kidney injury

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ABSTRACT

Cisplatin (CDDP) is a widely used anticancer drug, but acute kidney injury (AKI) is one of the most important dose-limiting factors. Trace metal elements are present in various concentrations in the body and play an important role in maintaining normal vital functions. However, the relationship between CDDP-induced AKI and trace metal elements is unknown. In this study, we cultured human renal proximal tubular epithelial cells in the presence of CDDP (0, 12.5, 25, 50 μM) and analyzed the concentration of trace elements in medium after 24 h. We found that CDDP significantly increased the concentrations of zinc (Zn) and manganese (Mn) in medium and significantly decreased them in lysate. Therefore, we examined the effects of CDDP (3 mg/kg, i.p.) administration on serum and urinary Zn and Mn concentrations in rats. The results showed that urinary excretion of Zn and Mn increased in CDDP-treated rats 5 days after administration. Also, 5 days after administration, pyknosis, nuclear loss, loss of the brush border membrane, and DNA fragmentation were observed, and serum creatinine and blood urea nitrogen levels were found to be significantly increased. These data suggested that 24-h excretion of Zn and Mn might reflect on CDDP induced nephropathy. Monitoring urinary Zn and Mn excretion may be beneficial in detecting AKI, but further studies are needed for clinical application.

1. Introduction

Cisplatin (CDDP) is an anticancer drug widely used to treat solid tumors including breast, cervical, esophageal, bladder, small cell lung, and testicular cancers. However, acute kidney injury (AKI) is observed in approximately 1–30% of patients treated with CDDP [1-4], and nephrotoxicity is one of the most important dose-limiting factors [3]. Renal damage caused by anticancer drugs affects the continuity of cancer treatment, patient's quality of life, and prognosis [3,5-7]. CDDP accumulates in the tubular epithelial cells and damages the proximal tubule [8]. CDDP accumulation induces inflammation, oxidative stress, vascular injury, endoplasmic reticulum stress, and necrosis and apoptosis of the renal tissue, thereby lowering glomerular filtration rate and causing AKI [8-10].

There are many trace metal elements in the human body at various concentrations, and they play an important role in maintaining normal vital functions [11-14]. Among the elements necessary for the maintenance of life function, those that are effective in small amounts are called essential trace metal elements. They are essential for the normal function of proteins and enzymes involved in physiological functions such as electron transfer and signal transduction, oxidation–reduction, storage and transport of oxygen molecules, expression of biocatalytic functions such as hydrolysis reactions, and gene expression, and the loss of homeostasis is associated with the occurrence of various diseases [15]. Although altered levels of these elements have been reported in several pathological conditions [16-18], it is still unclear which elements are altered in CDDP-AKI. If the changes in elemental levels in

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Abbreviations

AKI	acute kidney injury
BUN	blood urea nitrogen
CDDP	cisplatin
Co	cobalt
Cu	copper
Cr	chromium
Fe	iron
ICP-MS	inductively coupled plasma mass spectrometry
Mn	manganese
Mo	molybdenum
REGM	renal epithelial cell growth medium
RPTEC	human renal proximal tubular epithelial cells
SCre	serum creatinine
Se	selenium
ZIP8	Zrt, Irt-related protein 8
Zn	zinc

CDDP-AKI can be clarified, it may be possible to predict the onset of AKI by measuring elemental levels in biological samples. It may also assist in the development of prevention and treatment methods.

In this study, we aimed to determine the changes in elemental concentrations due to CDDP administration.

2. Materials and methods

2.1. Cell culture

Human renal proximal tubule epithelial cells (RPTEC, Lonza, Basel, Switzerland) were seeded and incubated in 6-well plates at 2.1×10^5 cell/well. Renal epithelial cell growth medium (REGM, Lonza, Basel, Switzerland) was used as the culture medium. After 24 h, CDDP (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) was added at final concentrations of 0, 12.5, 25, and 50 μM. After another 24 h, all the culture medium was collected. RPTEC were lysed by adding 2 mL of ultrapure water and freezing at −80 °C. Protein concentrations in medium and lysate were determined from the bicinchoninic acid assay. This experiment was conducted in three parallel runs.

2.2. Animals

This animal experiment was approved by the Ethics Committee of Nagoya City University (H29–P-05), and all experiments were conducted in accordance with the guidelines of the National Institute of Health Sciences of Japan.

Studies were performed on 8-week-old male Wistar-ST rats (Japan SLC Inc., Shizuoka, Japan). Six rats were included in each group: the control and CDDP administration groups. The protocol is shown in Fig. 1. In the CDDP-administered group, CDDP was intraperitoneally administered at a dose of 3 mg/kg, and in the control group, physiological saline was intraperitoneally administered. Urine samples were collected for 24 h in a urine collection cage from days 4–5. Blood samples were collected on day 5 (5 days after CDDP administration). Blood samples were collected from the inferior vena cava of the abdomen under anesthesia with isoflurane.

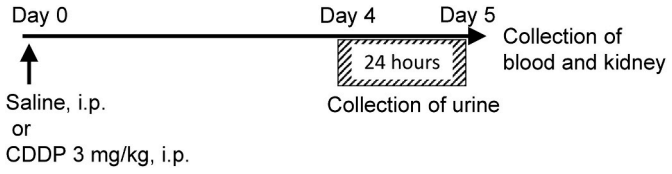

Fig. 1. Protocol for experiments with rats. On day 0, cisplatin or saline was administered intraperitoneally to 6 animals each, and urine was collected for 24-h from day 4 to day 5. On day 5, blood samples and renal tissue were obtained.

2.3. Element concentrations in medium, lysate, urine, and serum

The target elements were eight essential trace metal elements (chromium [Cr], manganese [Mn], iron [Fe], cobalt [Co], copper [Cu], zinc [Zn], selenium [Se], and molybdenum [Mo]) in medium and lysate, and Mn and Zn in urine and serum.

All elements were measured by inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7800 ICP-MS, Agilent Technologies, California, USA). The reagents used were nitric acid 1.38 (Kanto Chemical, Tokyo, Japan) and ICP-MS mixing standard XSTC-622 (SPEX CertiPrep, New Jersey, USA). Medium, lysate and urine were diluted 10-fold and serum was diluted 20-fold before analysis. (1 + 99) nitric acid was used as the diluent. For urine and serum, if they exceeded the calibration range, both were diluted 100-fold with (1 + 99) nitric acid. Equal amounts of yttrium standard solution (Kanto Chemical, Tokyo, Japan) were added to each test solution as an internal standard.

Since urinary concentrations of elements are affected by water intake, the amount of the element excreted in 24 h was evaluated. Urine specific gravity was determined using a digital urine specific gravity refractometer (UR-S, ATAGO, Tokyo, Japan), and 24-h excretion was calculated based on total urine volume and urine specific gravity. The 24-h excretion was normalized by body weight.

2.4. Kidney tissue staining image

Five days after CDDP administration, the renal tissue was removed, and after fixation with 10% formalin, a paraffin block was made. Renal tissue sections (5 μm) were prepared and stained with hematoxylin-eosin (HE), periodic acid Schiff (PAS)-hematoxylin. Detection of DNA fragmentation in renal tissue was performed by the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) method.

2.5. Serum creatinine and blood urea nitrogen concentrations

The measurement of serum creatinine (SCre) and blood urea nitrogen (BUN) concentrations was outsourced to FUJIFILM VET Systems Co, Ltd. (Tokyo, Japan).

2.6. Statistical analysis

Data are shown as mean ± standard deviation (S.D.). Data analysis of element concentrations in medium and lysate was performed using Dunnett's *t*-test, urinary element excretions, serum element concentrations, SCre, and BUN was performed using Welch's *t*-test. Differences were considered statistically significant at $P < 0.05$. Statistical analyses were performed with SPSS software package, version 17.0 (SPSS Inc., Chicago, USA) and EZR, version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [19].

3. Results

3.1. Element concentration in medium

The concentrations of the elements in medium are shown in Fig. 2. The concentrations of Zn and Mn in medium increased in dependence on the amount of CDDP added. The concentrations of Zn in medium were significantly higher at 25 and 50 μM than without CDDP ($P < 0.01$ and $P < 0.001$, respectively). The concentration was 107.62 ± 4.49 μg/L at 0 μM CDDP, compared to 125.74 ± 4.36 μg/L at 25 μM and 139.42 ± 3.26 μg/L at 50 μM. The concentration of Mn in medium was significantly

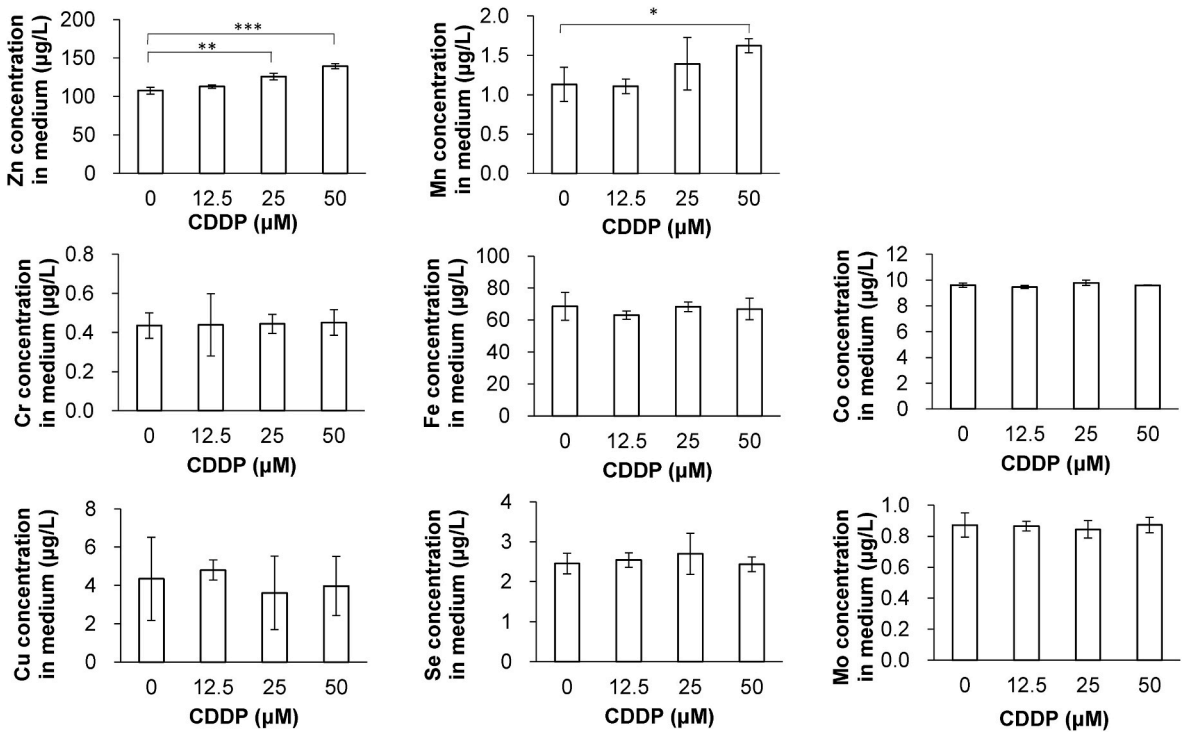

Fig. 2. Levels of elemental concentrations in medium. Data in each column are presented as the mean ± S.D. of 3 times. Concentrations of Zn and Mn in medium increased in a CDDP concentration-dependent manner. *P < 0.05, **P < 0.01, ***P < 0.001, indicating a statistically significant difference when compared to 0 μM (Dunnett's *t*-test).

higher at 50 μM than without CDDP (P < 0.05). The concentration was 1.13 ± 0.22 μg/L at 0 μM CDDP, compared to 1.62 ± 0.09 μg/L at 50 μM. No significant changes were observed for the other elements.

The results of normalizing the elemental concentrations in medium by the protein concentrations are shown in Supplemental Fig. 1. Of the three 0 μM samples, one sample was used up in the elemental concentration measurement, so the protein concentration could not be measured. Therefore, there were two 0 μM samples, and although statistical analysis could not be performed, but Zn and Mn concentrations increased in a CDDP dose-dependent manner as before normalization.

3.2. Element concentration in lysate

The concentrations of the elements in lysate are shown in Fig. 3. Cr, Se, and Mo were excluded because they were below the lower limit of quantification (0.20 μg/L). The concentrations of Zn and Mn in lysate decreased in dependence on the amount of CDDP added. The concentrations of Zn in lysate were significantly lower at 50 μM than without CDDP (P < 0.001). The concentration was 57.40 ± 11.45 μg/L at 0 μM CDDP, compared to 20.51 ± 4.75 μg/L at 50 μM. The concentration of Mn in lysate was significantly lower at 50 μM than without CDDP (P < 0.05). The concentration was 0.80 ± 0.12 μg/L at 0 μM CDDP, compared

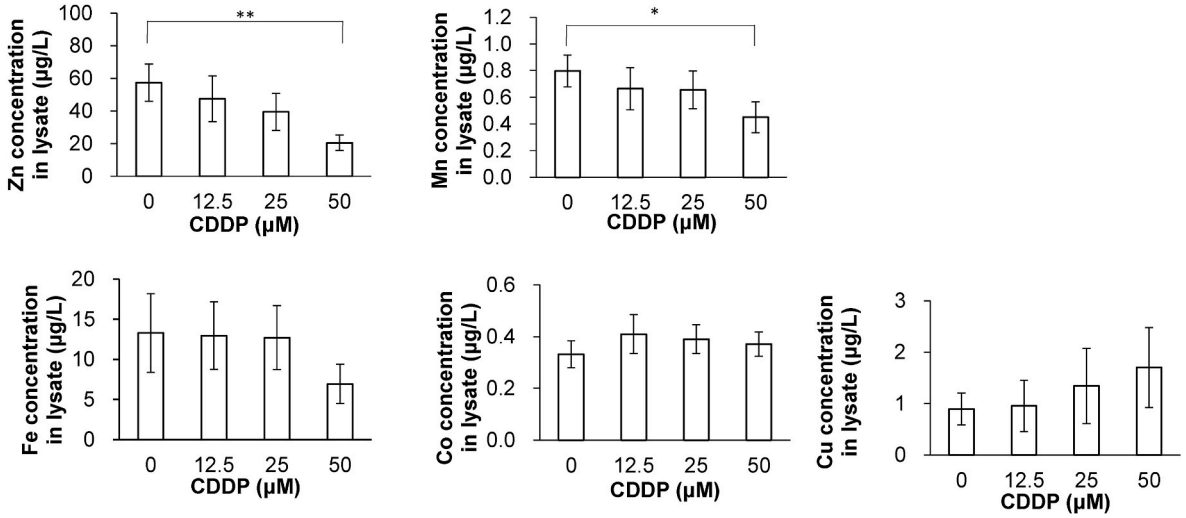

Fig. 3. Levels of elemental concentrations in lysate. Data in each column are presented as the mean ± S.D. of 3 times. Concentrations of Zn and Mn in lysate decreased in a concentration-dependent manner with CDDP. *P < 0.05, **P < 0.01, indicating a statistically significant difference when compared to 0 μM (Dunnett's *t*-test).

to 0.45 ± 0.12 μg/L at 50 μM. No significant changes were observed for the other elements.

The results of normalizing the elemental concentrations in lysate by the protein concentrations are shown in Supplemental Fig. 2. When normalized by protein concentration in lysate, the concentration difference due to CDDP administration was eliminated in Mn, but in Zn, the concentration of CDDP decreased in a dose-dependent manner as before normalization.

Therefore, we investigated the effect of CDDP administration on Zn and Mn in vivo.

3.3. Renal tissue staining

Staining images of renal tissues taken 5 days after the administration of saline (Control) and CDDP (3 mg/kg) are shown in Fig. 4. HE staining showed that CDDP caused pyknosis and nuclear loss of the proximal tubule, and necrosis was expected to occur. PAS staining showed that CDDP caused the loss of the brush border membrane. DNA fragmentation was detected by CDDP in the TUNEL assay, indicating that apoptosis had occurred.

3.4. Changes in SCre and BUN levels after CDDP treatment

Changes in SCre and BUN levels on day 5 are shown in Fig. 5. CDDP significantly increased both SCre and BUN levels on day 5. SCre was 1.70 ± 0.29 mg/dL for CDDP, which was significantly higher than the 0.38 ± 0.04 mg/dL for control ($P < 0.001$). BUN was 67.0 ± 10.9 mg/dL for CDDP, which was significantly higher than the 19.8 ± 2.1 mg/dL for control ($P < 0.001$).

3.5. Changes in the 24-h urinary excretion levels of trace elements

Plots of 24-h urinary Zn and Mn excretions in each sample are shown in Fig. 6. On day 5, CDDP caused a significant increase in the excretion of Zn and Mn compared with the levels of elements in control. Zn was 56.63 ± 14.79 μg/kg body weight for CDDP, which was significantly higher than the 21.58 ± 6.88 μg/kg body weight for control ($P < 0.01$). Mn was 28.11 ± 10.17 μg/kg body weight for CDDP, which was significantly higher than the 15.77 ± 3.77 μg/kg body weight for control ($P < 0.05$).

3.6. Changes in serum trace element concentrations

Plots of serum Zn and Mn concentrations in each sample are shown in Fig. 7. On day 5, Zn concentrations were 1.13 ± 0.14 μg/L for Control and 1.08 ± 0.09 μg/L for CDDP, with no significant difference. Mn concentrations were 3.78 ± 0.34 μg/L for Control and 3.67 ± 0.78 μg/L for CDDP, also with no significant difference.

4. Discussion

In the present study, we found that the addition of CDDP increased

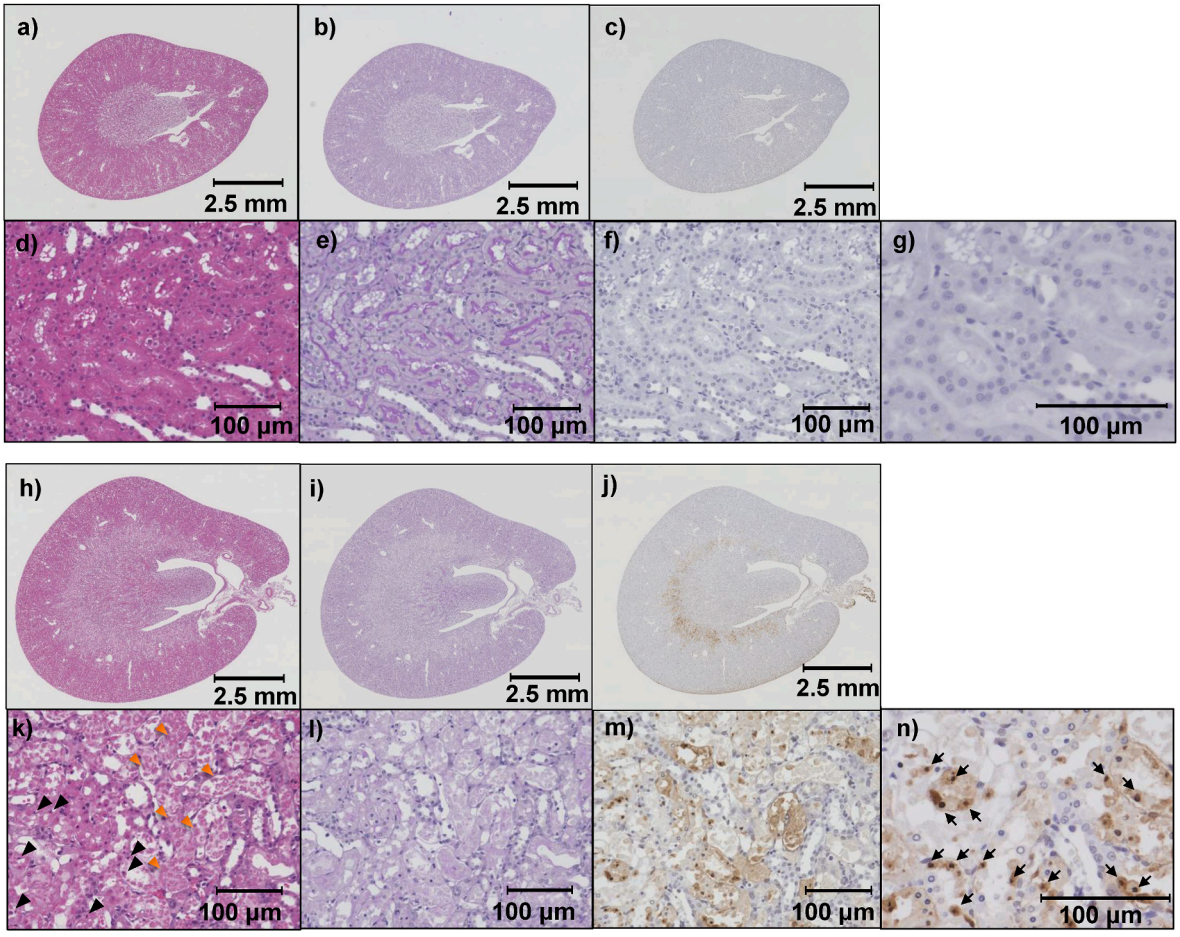

Fig. 4. Histological stained images of kidney tissue taken 5 days after administration of saline (Control) and cisplatin (CDDP). In the figures, a), b), c), d), e), f), and g) are Control, h), i), j), k), l), m), and n) are CDDP. a), d), h), and k) are HE stained images, black arrowheads indicate nuclear enrichment, orange arrowheads indicate nuclear loss. b), e), i), and l) are PAS stained images. c), f), g), j), m), and n) are TUNEL assay images. g) is a partially enlarged version of f) and n) is a partially enlarged version of m). Black arrows indicate DNA fragmentation. Six animals were stained with Control and CDDP, respectively, and one representative example is shown. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

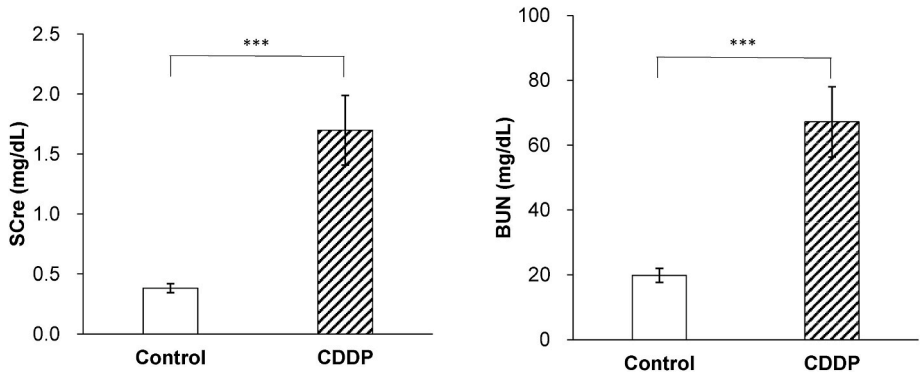

Fig. 5. Serum creatinine (SCre) and blood urea nitrogen (BUN) levels on 5 days after the administration of saline (Control) or cisplatin (CDDP). Data in each column are presented as mean ± S.D. of 6 animals. Both SCre and BUN concentrations were significantly elevated after 5 days of CDDP administration compared to Control. ***P < 0.001, indicates statistically significant differences when compared to the control (Welch's *t*-test).

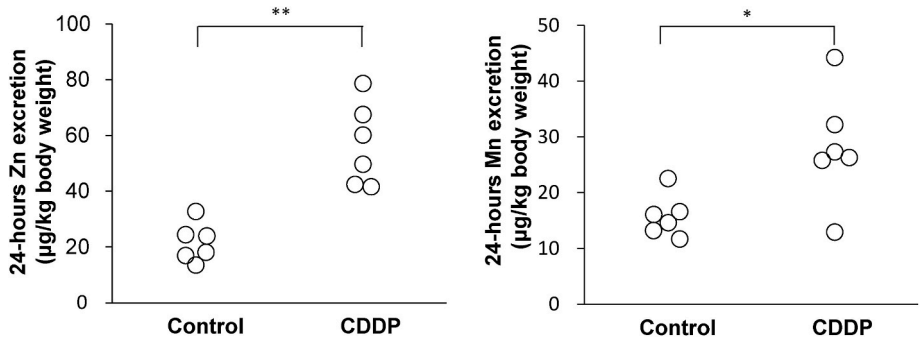

Fig. 6. Plots of 24-h urinary zinc (Zn) and manganese (Mn) excretion levels in each sample. Each plot shows the 24-h urinary Zn and Mn excretion levels of 6 animals. 24-hour urinary excretion of Zn and Mn were both significantly elevated after 5 days of CDDP administration compared to the Control. *P < 0.05, **P < 0.01, indicates statistically significant differences when compared to the control (Welch's *t*-test).

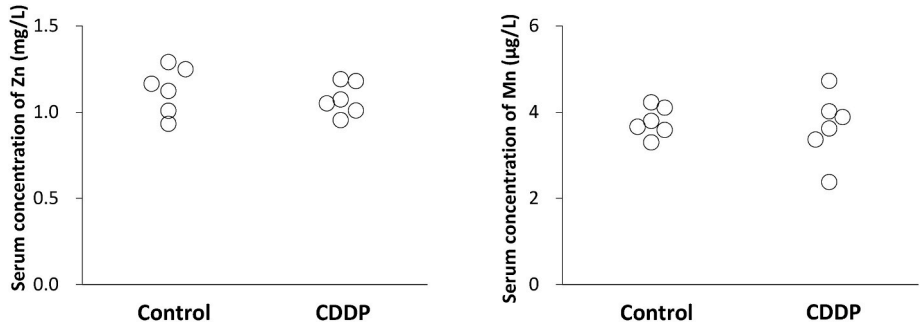

Fig. 7. Plots of serum zinc (Zn) and manganese (Mn) concentrations. Each plot shows the serum Zn and Mn concentrations of 6 animals. No significant difference was observed in serum Zn and Mn concentrations 5 days after CDDP administration compared to Control (Welch's *t*-test).

the concentrations of Zn and Mn in medium in which RPTEC were cultured and decreased the concentrations of Zn and Mn in lysate. The 24-h urinary Zn and Mn excretion levels altered in rats receiving CDDP treatment, suggesting that Zn and Mn were released from the cells by CDDP. HE staining of kidney tissue from rats treated with CDDP showed pyknosis and loss of nuclei, indicative of CDDP-induced necrosis. PAS staining showed loss of brush border membrane. TUNEL assay revealed DNA fragmentation, and apoptosis was determined to have occurred. In addition, SCre and BUN were significantly elevated, indicating impaired renal function. Thus, the changes in 24-h urinary excretion of Zn and Mn due to CDDP treatment may reflect CDDP-induced dysfunction of the brush border membrane. Monitoring urinary excretion of Zn and Mn during CDDP administration may help detect AKI when urinary excretion of Zn and Mn increases. Although Zn and Mn are thought to be released from the cells as a consequence of cell death, changes in medium concentrations were specific to Zn and Mn, with no significant changes were observed for the other elements. This suggests that there may be dysfunctional or other effects as well as effects of intracellular release due to cell death.

Zn is normally excreted in small amounts in urine because it is efficiently reabsorbed in the renal tubules [20]. This reabsorption is mediated by zinc transporters expressed in the tubules, and Zrt, Irt-related protein 8 (ZIP8), a type of zinc transporter, may also play an important role in Mn reabsorption in the renal tubules [21,22]. It is possible that CDDP-induced damage to the proximal tubules inhibits not only Zn but also Mn reabsorption.

It is not known whether other anticancer drugs or other nephrotoxic drugs also increase urinary Zn and Mn levels. Methotrexate, used as an

anticancer drug, also causes renal injury, reportedly due to obstructive damage caused by drug precipitation in the tubular lumen; beta-lactam antibiotics are reported to cause interstitial nephritis [23]. Thus, different drugs have different mechanisms of renal injury, and the kinetics of elemental concentrations may also differ.

In this study, 24-h urinary excretion of Zn and Mn increased, but serum concentrations of Zn and Mn did not change, suggesting that Zn and Mn in vivo are not deficient. Thus, Zn and Mn supplementation is not expected to reduce nephrotoxicity.

This study was conducted in laboratory animals and may reflect only the effects of CDDP. In the clinical setting, there may be high individual differences owing to patients' background characteristics such as sex, age, complications, medicine, and dietary effects. Therefore, further studies are needed to determine if changes in urinary Zn and Mn concentrations are observed in humans with CDDP-induced AKI.

In conclusion, in the present study, CDDP administration increased Zn and Mn concentrations in medium of RPTEC and decreased in lysate. In addition, urinary Zn and Mn excretion increased. These changes may reflect injury of the brush border membrane in CDDP-AKI. Monitoring urinary Zn and Mn excretion may be beneficial in detecting AKI, but further studies are needed for clinical application.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2023.101422.

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