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[Original Article]

## CORRELATIONS AMONG HEAVY METALS IN BLOOD AND URINE AND THEIR RELATIONS TO DEPRESSIVE SYMPTOMS IN PARKINSON'S DISEASE PATIENTS

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**Abstract : Objectives :** From our previous results, manganese (Mn) and iron (Fe) in the blood of Parkinson's disease (PD) patients without depression were higher than those of both the PD patients with depression and controls, the hypothesis that "two types of PD exist-PD without depression and affected by Mn and Fe, and PD with depression and unaffected by Mn or Fe" was induced. To investigate the hypothesis, correlations among blood and urine metals were compared in the subjects. **Methods :** Subjects comprised PD patients with depression, PD patients without depression and controls recruited from an outpatient clinic in China. Morning blood and urine samples were used to measure concentrations of metals. **Results :** In the controls, Mn, Fe and zinc (Zn) levels in blood strongly correlated with each other. The correlation coefficient between Mn and Zn in blood was significant in the PD patients with depression and the controls, but not in the PD patients without depression. Correlations of Fe between blood and urine in the PD patients without depression were significant, but not in the PD patients with depression and the controls. **Conclusions :** A common route of simultaneous intake of Mn, Fe and Zn could exist in our subjects, however in PD patients without depression, a large intake of Mn may have been from another route. Some results of the PD patients without depression were different from those of the PD patients with depression and the controls. Thus, two types of PD may exist.

**Key words :** Parkinson's disease, Depression, Heavy metals, Correlation, Blood and urine levels

### INTRODUCTION

Manganese (Mn) poisoning is well known to result in Parkinsonian symptoms<sup>1</sup>. A case of Mn-induced human parkinsonism caused by excess accumulation of Mn in daily life has been reported<sup>2</sup>. A previous study also revealed that a high intake of iron (Fe), especially in combination with high Mn intake, might be related to risk of idiopathic Parkinson's disease (PD)<sup>3</sup>. Idiopathic PD and Parkinsonian syndrome caused by Mn poisoning are known to be indistinguishable in terms of symptoms, and

we suspect that many patients, who have accumulated Mn in the body in daily life, are being diagnosed as having idiopathic PD rather than Mn poisoning. Furthermore, some heavy metals may be involved in the etiology of idiopathic PD.

Some reports have suggested the role of heavy metals in human depression. In those studies, Fe<sup>4</sup> and Copper (Cu)<sup>5</sup> appeared to be deficient in subjects with depression, and low dietary or supplemental zinc (Zn) intake was more likely to cause depressive symptoms<sup>6</sup>. Depression is common in PD, and approximately 30-40% of PD patients have sig-

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nificant depressive disorders<sup>7</sup>. Lemke *et al.*<sup>8</sup>) reported anxiety and depression as risk factors for development of PD, possibly being present many years before the appearance of motor symptoms. Bower *et al.*<sup>9</sup>) studied the association of three personality traits related to neuroticism with a subsequent risk of PD. Sanyal *et al.*<sup>10</sup>) also reported that a previous history of depression was associated with increased risk of PD. These studies suggested that depression might predict an increased risk of PD developing many years later, and common background may exist in the etiology of both PD and depression.

In our previous study<sup>11</sup>), whole-blood Mn levels were significantly higher in PD patients without depression than those in both PD patients with depression and the controls. Serum Fe levels were significantly higher in the PD patients without depression than those in the controls. Urine Fe levels were also significantly higher in the PD patients without depression than those in the controls. Excessive intake of Fe and accumulation of Mn seemed to be involved in the etiology of non-depressive PD. Two types of PD may possibly exist, PD without depression affected by Mn and Fe and PD with depression not affected by Mn or Fe. In the former type, Mn and Fe may affect PD and depression onset individually, that is, Mn and Fe may be involved in the etiology of PD, however, simultaneously, Fe may have protective effects against depression. However, it was unknown why Mn and Fe in the blood of PD patients without depression were higher than those of other two groups. The PD patients without depression may have a route of simultaneous or special intake of Mn and/or Fe unlike other two groups. If it becomes clear, this hypothesis can be supported more strongly. In the present study, correlation coefficients were calculated among blood and urine metals to investigate the hypothesis.

## METHODS

The subjects were the same as those in our previous report<sup>11</sup>), comprising 19 PD patients with depression (9 men, 10 women; mean age=63.3±10.2 years), 52 PD patients without depression (31 men, 21 women; mean age=63.9±9.6 years) and 70 controls (41 men, 29 women; mean age, 63.4±9.7 years). All subjects were recruited from the outpatient clinic of Xiangfan No. 1 People's Hospital in Hubei, China between 2006 and 2008. The controls were matched regarding sex and age (±3 years), had no PD or depression, but symptoms such as headache and dizziness. In the previous study

with the same subjects, no differences were seen in intake of each metal, energy, protein, fat, carbohydrate or dietary fiber between the PD patients and the controls<sup>12</sup>).

PD was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank<sup>13</sup>). Depressive status was assessed simultaneously with PD diagnosis in the first medical examination by trained neurologists in Xiangfan No. 1 People's Hospital. DSM-IV criteria<sup>14</sup>) was used for the primary diagnosis of a depressive disorder. Major depression and dysthymia were our outcomes of interest. Severity of depression in patients was assessed using the Hamilton Depression Rating Scale (HAMD-17)<sup>15</sup>), and a score of ≥14 was defined as "depression"<sup>16</sup>).

All PD patients and controls were examined by neurologists from the clinic, and underwent computed tomography inspection. We excluded those whose parkinsonism was possibly secondary to stroke or others, as well as those who had a history of stroke or others. Written informed consent was obtained from all subjects and the study protocol was approved by the ethics boards of Xiangfan No. 1 People's Hospital and Fukushima Medical University.

Morning blood and urine samples were collected before breakfast and used to measure concentrations of Mn, Fe, Cu and Zn. Serum and urine Fe, Cu and Zn were measured by inductively coupled plasma atomic emission spectrometry. Whole-blood and urine Mn were determined by atomic absorption spectrometry. The measurements were done in the Research Center of Wuhan University School of Medicine according to the standard protocol of Wuhan University for the laboratory data.

The SPSS statistical package was used. Pearson's correlation coefficient was calculated among blood and urine metals, and significance probability was judged by the two-sided test. Differences in sex among groups were assessed using the  $\chi^2$  test for bivariate analysis. Means for age were analyzed using analysis of variance. The significance level was set at 0.05.

## RESULTS

No differences were observed in sex and age among the three groups.

The correlations of each metal concentration in blood in the subjects are shown in Fig. 1. The correlation coefficients between blood Mn (MnB) and blood Fe (FeB) of the PD patients with depression, PD patients without depression and controls were

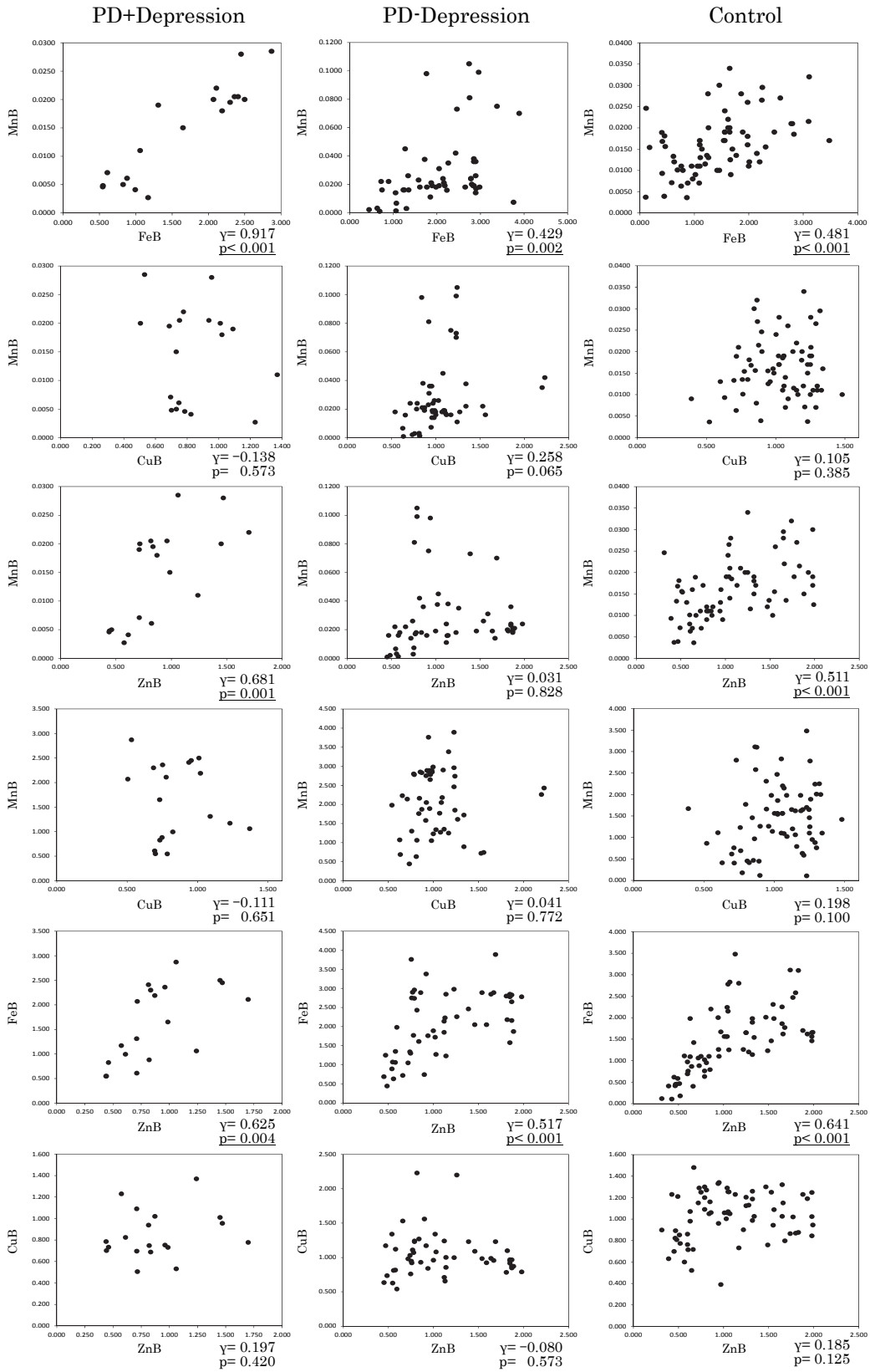


Fig. 1. Correlations of each metal concentration in blood in the subjects  
MnB :  $\mu\text{g/ml}$  (whole blood) ; FeB, CuB, ZnB :  $\mu\text{g/ml}$  (serum)  
Underline was drawn to the  $p$  value significant correlation was found.  
PD+depression, PD patients with depression ; PD-depression, PD patients without depression ; Control, control subjects

0.917 ( $p < 0.001$ ), 0.429 ( $p = 0.002$ ) and 0.481 ( $p < 0.001$ ), respectively, and were significant. The correlation coefficients between FeB and blood Zn (ZnB) of the PD patients with depression, PD patients without depression and controls were 0.625 ( $p = 0.004$ ), 0.517 ( $p < 0.001$ ) and 0.641 ( $p < 0.001$ ), respectively, and were also significant. The correlation coefficients between MnB and ZnB in the blood of the PD patients with depression and the controls were significant, at 0.681 ( $p = 0.001$ ) and 0.511 ( $p < 0.001$ ), respectively, but that of the PD patients without depression was 0.031 ( $p = 0.828$ ), and was not significant. In the controls, MnB, FeB and ZnB were correlated each other strongly. Blood Cu (CuB) was not correlated with MnB, FeB or ZnB in the three groups.

The correlations of each metal concentration in urine in the subjects are shown in Fig. 2. The correlation coefficients between urine Mn (MnU) and urine Fe (FeU) of the PD patients without depression and the controls were 0.331 ( $p = 0.017$ ) and 0.284 ( $p = 0.017$ ), respectively, and were slightly significant, but that of the PD patients with depression was 0.226 ( $p = 0.351$ ), and was not significant. The correlation coefficients between FeU and urine Cu (CuU) of the PD patients with depression and the controls were 0.571 ( $p = 0.011$ ) and 0.293 ( $p = 0.014$ ), respectively, and were also slightly significant, but that of the PD patients without depression was 0.111 ( $p = 0.432$ ), and was not significant. Additionally, the correlation coefficient between CuU and urine Zn (ZnU) of the PD patients without depression was slightly significant at 0.302 ( $p = 0.029$ ), but those of the PD patients with depression and the controls were not significant, at 0.133 ( $p = 0.587$ ) and 0.159 ( $p = 0.189$ ), respectively.

Correlations of each metal between blood and urine concentrations in the subjects are shown in Fig. 3. The correlation coefficient of Fe in the PD patients without depression was 0.305 ( $p = 0.028$ ), and was slightly significant, however those in the PD patients with depression and the controls were 0.218 ( $p = 0.370$ ) and 0.219 ( $p = 0.069$ ), respectively, and were not significant.

## DISCUSSION

The mechanism of neurotoxicity of Mn and Fe is thought as follows. 1-methylnicotinamide (MNA) is produced via nicotinamide N-methyltransferase (EC 2.1.1.1) (NNMT) from nicotinamide. PD patients had higher levels of NNMT activity and protein in brain tissue than controls<sup>17</sup>. MNA de-

stroyed several subunits of cerebral complex I, especially 30 kDa protein<sup>18</sup>, and MNA injection in rat substantia nigra pars compacta significantly decreased dopamine content in striatum<sup>19</sup>. Therefore, MNA is suspected as an agent causing idiopathic PD. It has been suggested that NNMT activity is affected by the presence of heavy metals, such as Mn and Fe. By the subsequent research we clarified Mn increased NNMT activity<sup>20</sup>. Daily intake of Mn and Fe may thus contribute to idiopathic PD.

The correlation coefficients between MnB and FeB, and between FeB and ZnB were significant in all groups. The correlation coefficients between MnU and FeU of the PD patients without depression and the controls were slightly significant, but that of the PD patients with depression was not significant. This might be due to the limited number of PD patients with depression participating in this study. These patients, however, had the same tendency as those in the other groups. In the controls, MnB, FeB and ZnB were strongly correlated with each other. From these results, a route of simultaneous intake of Mn, Fe and Zn could exist in the subjects. Furthermore, because in the three groups, CuB was not correlated with MnB, FeB or ZnB, a different route of Cu intake from other metals might exist.

Some results of the PD patients without depression were different from those of the PD patients with depression and the controls. The correlation coefficient between MnB and ZnB was significant in both the PD patients with depression and the controls, but not in the PD patients without depression. Because we found in our previous report that whole-blood Mn was significantly higher in the PD patients without depression than in both the PD patients with depression and controls<sup>11</sup>, the PD patients without depression might have taken a large amount of Mn from a route different from the one common to Mn, Fe and Zn. In the present study, the correlation coefficient between FeU and CuU was also significant in the PD patients with depression and the controls, but not in the PD patients without depression. The correlation coefficient between the CuU and ZnU of the PD patients without depression was significant, but those of the PD patients with depression and the controls were not significant. Although it was unknown why the difference in Fe, Cu and Zn was not observed in blood but in urine, it seemed that the metabolisms of Fe, Cu and Zn in the PD patients without depression was different from those in both the PD patients with de-

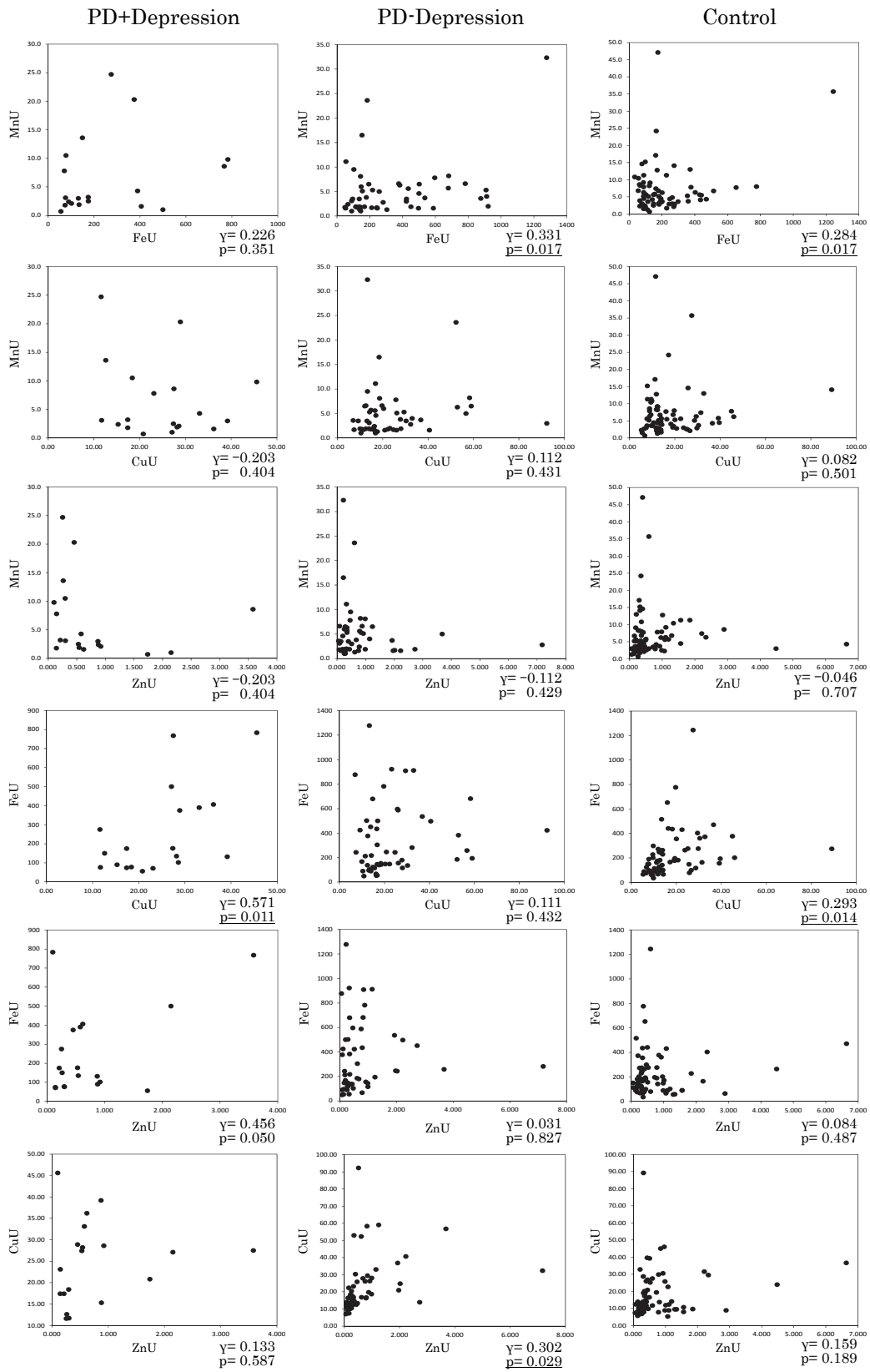


Fig. 2. Correlations of each metal concentration in urine in the subjects  
MnU, FeU, CuU :  $\mu\text{g/l}$ ; ZnU :  $\text{mg/l}$   
Underline was drawn to the  $p$  value significant correlation was found.  
PD+depression, PD patients with depression ; PD-depression, PD patients without depression ; Control, control subjects

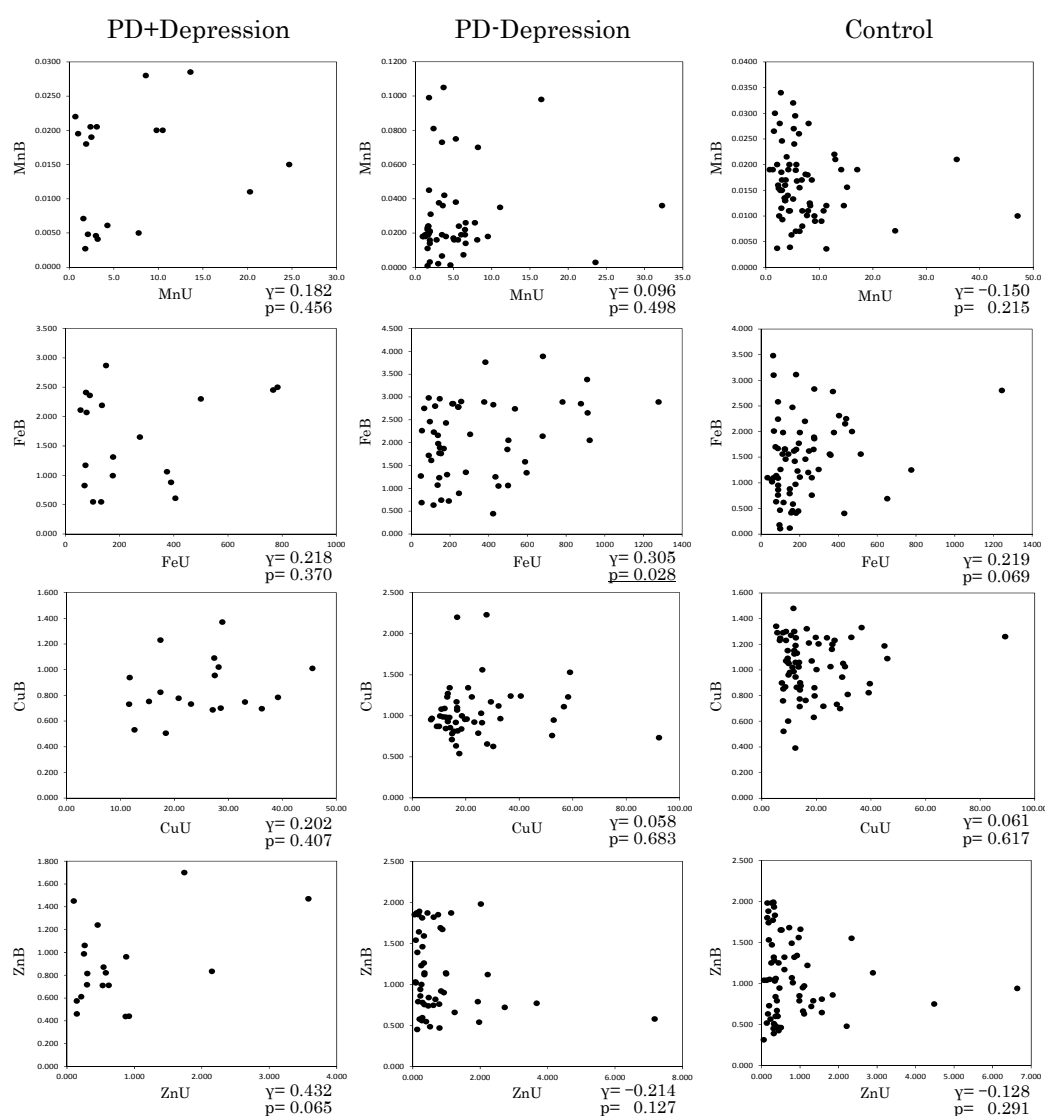


Fig. 3. Correlations of each metal between blood and urine concentrations in the subjects  
 MnB :  $\mu\text{g/ml}$  (whole blood) ; FeB, CuB, ZnB :  $\mu\text{g/ml}$  (serum) ; MnU, FeU, CuU :  $\mu\text{g/l}$  ; ZnU :  $\text{mg/l}$   
 Underline was drawn to the  $p$  value significant correlation was found.  
 PD+depression, PD patients with depression ; PD-depression, PD patients without depression ; Control, control subjects

pression and the controls.

Correlations of Fe between blood and urine concentrations in the PD patients without depression were significant, but not in the PD patients with depression and the controls. In our previous study, both serum and urine Fe were significantly higher in the PD patients without depression than in the controls<sup>11)</sup>. Excessive intake of Fe in daily life could be related to the pathogenesis of PD without depression. Because Fe deficiency commonly co-occurred with depressive symptoms in older people<sup>21)</sup>, Fe might function as a pathogenic factor in PD, while simultaneously being protective against depression. As another possible reason why the PD

patients without depression is not accompanied by depression, confounding factors other than Fe may exist, or it may be a type of PD that is not accompanied by depression from onset because of a different etiology from the PD patients with depression. Further study is needed to verify the meaning of Fe on the etiology of PD without depression.

In conclusion, a common route of simultaneous intake of Mn, Fe and Zn could exist in our subjects, however in PD patients without depression, a large intake of Mn may have been from another route. Some results of the PD patients without depression were different from those of the PD patients with depression and the controls. Two types

of PD may exist, PD without depression affected by Mn and Fe, and PD with depression not affected by Mn and Fe. In the PD patients without depression, each metal may affect PD and depression onset individually, thus Mn and Fe could be pathogenic to PD, but Fe might be protective against depression. However, there may be a type of PD that is not accompanied by depression from onset. PD whose etiology is neither affected by Mn nor Fe and is accompanied by depression may be able to be called idiopathic PD in a narrow sense.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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