on medications that may affect uric acid levels or CKD risk, including losartan, diuretics, fibrates and nonsteroidal anti-inflammatory drugs, and the presence of metabolic syndrome as defined by ATP III criteria. We found the odds ratios to be attenuated suggesting the presence of some confounding by these factors. However, the original finding in our paper [1] of a positive association between serum uric acid and CKD remained the same.

Second, Dr Solak mentions that the observed association between serum uric acid and CKD in our paper may be due to the metabolic syndrome. To examine this hypothesis, we additionally adjusted for metabolic syndrome as a covariate in the multivariable model (see the multivariable model 2 in Table 1). We found the odds ratios to be slightly attenuated suggesting the presence of some confounding by metabolic syndrome. However, the original finding in our paper [1] of a positive association between serum uric acid and CKD remained the same.

Third, Dr Solak mentions that the observed association between serum uric acid and CKD in our paper may be due to different patterns of drug use or dietary patterns, including fructose intake. To examine the role of different patterns of drug use, we additionally adjusted for the use of losartan, diuretics, fibrates and nonsteroidal anti-inflammatory drugs as a covariate in the multivariable model (see the multivariable model 2 in Table 1). We found the odds ratios to be slightly attenuated, but the original conclusion from our study [1] of a positive association between serum uric acid and CKD remained robust. Unfortunately, we did not have data on dietary factors to examine the role of fructose intake as a confounder.

Fourth, Dr Solak suggests the use of an estimated glomerular filtration rate (eGFR) cutoff instead of a serum creatinine cutoff to perform the sensitivity analysis. To address this point, we have now performed a new sensitivity analysis excluding subjects with eGFR values <30 mL/min/1.72 m². Here we found the odds ratios to be slightly accentuated, and the original conclusion from our study [1] of a positive association between serum uric acid and CKD remained robust.

In conclusion, within reasonable limits, we have shown that our findings [1] of a positive association between serum uric acid and CKD remained robust even after multiple sensitivity analyses. We agree with Dr Solak that data from longitudinal studies are needed to confirm this association.

Conflict of interest statement. None declared.

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Peritoneal clearance and transport of methylglyoxal

Sir,

Methylglyoxal (MG), a chemically reactive 72-Da α-oxoaldehyde, is recognized to be one of the main culprits of local peritoneal damage in peritoneal dialysis (PD) patients in the era of high-glucose degradation products (GDPs) solution, as Hirahara et al. showed in a recent Nephrology Dialysis Transplantation article [1]. This compound, however, has been recently recognized as one of the main culprits of cardiovascular disease (CVD) in all stages of chronic kidney disease (CKD) patients. Plasma MG levels increase as the CKD stages progress, and significantly higher MG levels were observed in patients with a CVD history compared with those without [2]. Reportedly, the plasma MG level is also elevated in PD patients [3]. If so, it is important to clarify peritoneal clearance and transport of MG, for a high level of plasma MG could induce transfer to the peritoneal cavity, and as a result, local peritoneal damage might be induced.

To clarify this issue, we conducted a study comparing peritoneal MG transport with that of creatinine (Cr, 113 Da), a dialysable substance of similar molecular weight not produced locally in the peritoneal cavity. Fourteen patients (10 males and 4 females) 63.9 ± 11.7 years of age, treated by PD using a neutral low-GDP solution for an average of 54.5 ± 46.8 months were investigated. Dialysate

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Table 1. Association between serum uric acid levels and chronic kidney disease (CKD)

<table>
<thead>
<tr>
<th>Multivariable models</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariable model in the paper</td>
<td>1 (referent)</td>
<td>1.53 (1.31–1.78)</td>
<td>2.16 (1.86–2.50)</td>
<td>4.67 (4.07–5.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable model a</td>
<td>1 (referent)</td>
<td>1.52 (1.31–1.76)</td>
<td>2.09 (1.79–2.44)</td>
<td>4.27 (3.98–4.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Including those with eGFR &lt;30 mL/min/1.72 m²</td>
<td>1 (referent)</td>
<td>1.55 (1.33–1.81)</td>
<td>2.18 (1.88–2.53)</td>
<td>4.56 (3.96–5.24)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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aEstimated from multivariable logistic regression model adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, all others), education categories (< high school, high school, > high school), smoking (never, former, current), alcohol intake (never, former, current), body mass index (normal, overweight, obese), diabetes (absent, present), hypertension (absent, present) and serum cholesterol (mg/dL).

bAdditional adjusting for the use of losartan, diuretics, fibrates and nonsteroidal anti-inflammatory drugs as a covariate in the multivariable model (see the multivariable model 2 in Table 1). We found the odds ratios to be slightly accentuated, but the original conclusion from our study [1] of a positive association between serum uric acid and CKD remained the same.

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Conflict of interest statement. None declared.
samples (10 mL) were obtained from a bag after the completion of the fast peritoneal equilibration test (fast PET) [4].

MG was determined by electrospray ionization liquid chromatography/mass spectrometry (ESI/LC/MS), as previously reported [2]. Plasma and dialysate effluent levels of Cr and beta 2-microglobulin (β2-m), one of the representative middle-sized dialysable molecules (11 800 Da), were also measured using standard laboratory techniques. Differences between the two groups were tested using Student’s t-test. Correlations between the variables were tested using Spearman’s test. The study protocol was approved by a local institutional review board, and all study participants signed informed consent before joining the study.

The MG concentrations in plasma were 975 ± 663 (range, 376–2815) nmol/L, which was far higher than that of normal subjects (149 ± 17 nmol/L, P < 0.0001) [2]. The MG concentration of dialysate effluent level was 294 ± 184 (range, 127–838) nmol/L, which was strongly correlated with that of plasma (r = 0.944, P < 0.0001). The MG level of dialysate effluent was significantly higher than that of plasma of normal subjects (P = 0.0017). When comparing peritoneal permeability for MG and Cr, we noted a strong positive correlation between D/P ratios of MG and Cr after the fast PET (Figure 1; r = 0.881, P < 0.0001). There was also a significant positive correlation between D/P ratios of MG and β2-m (r = 0.705, P = 0.0055), while its correlation is somewhat weaker than that of MG and Cr.

Similar characteristics of peritoneal transport of MG and Cr might suggest that MG enters the dialysis fluid from the systemic circulation just like Cr does. It is supposed that effluent MG transferred from plasma could induce local peritoneal damage. Dialysate lacks defence mechanisms to MG such as the glyoxalase system and various anti-oxidants, which are highly present in whole blood. Therefore, we believe that special attention should be paid to MG even in the era of low-GDP solutions.

**Conflict of interest statement.** None declared.

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**Fig. 1.** The relationship between D/P ratios of methylglyoxal and creatinine after the fast PET.

\[ R = 0.881 \quad P = 0.0001 \]

\[ \text{D/P-MG} = -0.102 + 0.743 \times \text{D/P-Cr}; R^2 = 0.776 \]

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**Reply**

Sir,

Methylglyoxal (MG) is an extremely toxic glucose degradation product (GDP) that is generated as a result of the degradation of glucose in peritoneal dialysis (PD) fluid during heat sterilization and storage. It is also produced as a metabolite from glucose in vivo. We previously showed that MC, which is contained in conventional PD fluid, is a risk factor as a cause of peritoneal injury in patients undergoing PD [1, 2]. It has long been debated whether GDPs in peritoneal effluent are derived from the circulation in addition to PD fluid. The present study by Terawaki et al. showed the possibility that most MG is transferred from the circulation to the peritoneal cavity in patients using new low-GDP PD fluid, by analysis of dialysate/plasma (D/P) ratios of MG and creatinine levels. D/P ratios are usually analyzed to check the peritoneal permeability of small solutes and are often examined to confirm whether the object materials in peritoneal effluent are derived from the circulation [3]. In their present study, the MG level of peritoneal effluent was 0.294 ± 0.184 (range, 0.127–0.838) μM when using new low-GDP PD fluid. We previously confirmed that a safe MG level without a risk of peritoneum injury is <0.8 μM from the results of permitted daily exposure analysis [1]. On the other hand, Rippe et al. reported that MG levels of conventional PD fluids were 22.7–33.3 μM and that those of new PD fluids were <2.8 μM, and the levels of many peritoneal injury biomarkers are significantly different between PD patients using conventional PD fluid and patients using new low-GDP fluid