Is Concomitant Therapy with Acetaminophen and Low-dose Aspirin a Risk Factor for CKD Progression? A 6-Year Cohort Study

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Concomitant therapy with acetaminophen (APAP) and low-dose aspirin is often used in clinical settings; however, it is unclear whether this combination is involved in the progression of chronic kidney disease (CKD). We hypothesized that concomitant therapy with APAP and low-dose aspirin may cause CKD progression. We carried out a retrospective 6-year cohort study that included all patients who received low-dose aspirin from January 2011 to December 2016 at Kaetsu Hospital. Primary outcome was defined as CKD progression at the end of the study compared with baseline. Among the 441 patients treated during the study period, we identified 89 cases of CKD progression. Multivariate regression analysis showed that exposure to APAP > 50 g [odds ratio (OR), 2.68, 95% confidence interval (CI), 1.08–6.70], age increase by 1 year (OR, 1.05, 95% CI, 1.02–1.08), and diabetes mellitus (OR, 2.40, 95% CI, 1.41–4.08) had positive associations with CKD progression. Our findings suggested that concomitant therapy with APAP and low-dose aspirin increased the risk of CKD progression. Therefore, we recommend more thorough monitoring of serum creatinine when patients are on such concomitant therapy. Moreover, it is important to advise users of low-dose aspirin to avoid unnecessary use of APAP, in order to reduce the risk of CKD progression.

Key words — acetaminophen; aspirin; chronic kidney disease; concomitant

INTRODUCTION

Drug-induced kidney disease (DIKD) is an important cause of kidney injury (KI). However, no standards have yet been established to identify drug-induced nephrotoxicity; thus, DIKD often goes unrecognized.1) Prevention, early detection, and prompt treatment of DIKD are critical to prevent progression to chronic kidney disease (CKD) and the development of kidney failure.2)

Although monotherapy with acetaminophen (APAP) or aspirin is not associated with CKD progression, concomitant therapy with APAP and aspirin is associated with kidney failure.3–5) In addition, daily use of analgesic mixtures containing both aspirin and APAP produced renal papillary necrosis in female rats,6) and is associated with analgesic nephropathy in humans.7) Thus, concomitant therapy with APAP and aspirin may be associated with risk of CKD progression. Low-dose aspirin is an anti-platelet agent recognized for its use in the secondary prevention of occlusive vascular events in the heart and brain.8) Furthermore, APAP has long been used as an analgesic in chronic pain conditions.9,10) Hence, concomitant therapy with APAP and low-dose aspirin is often used in clinical settings; however, it is unclear whether this combination increases CKD risk. The objective of this study was to evaluate the influence of concomitant therapy with APAP and low-dose aspirin on CKD progression.

PATIENTS AND METHODS

Study Design and Definitions We conducted a retrospective 6-year cohort study that included all patients who received low-dose aspirin (81–100 mg/d, the standard doses in Japan) from January 2011 to December 2016 at Kaetsu Hospital. Baseline and end of study parameters were assessed in 2011 and 2016. We collected the following data: sex, age, body weight (BW), serum creatinine, hemoglobin A1c, total cholesterol, low-density lipoprotein, prescription periods for APAP and nonsteroidal anti-inflammatory drugs (NSAIDs), basal disease, and all medications. APAP was assessed in terms of the total degree of exposure during the study period, because the dose usually changes in the clinical setting.
We excluded patients who had nephritis or kidney cancer, those for whom serum creatinine measurements were not available, CKD stage 5, and history of NSAID prescription. CKD as a clinical outcome was defined as progression of CKD stage at the end of the study compared with baseline. Diabetes mellitus (DM) was defined as the need for insulin or an oral hypoglycemic drug. Hypertension (HT) was defined as the need for an antihypertensive drug. CKD stage was defined according to Kidney Disease Outcome Quality Initiative (KDOQI) criteria and the estimated glomerular filtration rate (eGFR) was calculated using the Japanese equation for GFR estimation. The study was approved by the institutional review board of Kaetsu Hospital (Approval number H29-013) and was conducted in accordance with the Helsinki Declaration.

To assess the association between CKD progression and APAP exposure, we first evaluated patient characteristics classified on the basis of APAP exposure. Next, to assess the cause of CKD progression, we evaluated patient characteristics classified on the basis of CKD progression. Last, multivariate modeling was performed to identify the independent factors associated with CKD progression. Explanatory variables were selected as significant factors from among patient characteristics classified on the basis of CKD progression in addition to APAP exposure. However, angiotensin-converting enzyme (ACE) inhibitor use was excluded in the multivariate analysis because it is empirically used to improve renal outcome in CKD patients.

**Statistical Analysis** All analyses were performed with R 3.4.1 (R Foundation for Statistical Computing, Vienna). Continuous variables were reported as median and range, and categorical variables were reported as frequencies and percentages. Univariate analysis was performed using Mann-Whitney U and Fisher exact tests. \( p < 0.05 \) was considered statistically significant. Multivariate modeling was performed using logistic regression analysis to identify the independent factors associated with CKD progression. We included APAP exposure, CKD stage, age, and DM as variables for the analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the multivariate analyses. APAP exposure was used as a categorical, but not a continuous variable, in the multivariate analyses because low APAP exposure was not considered a risk factor for CKD progression.

**RESULTS**

In this study, 677 patients received low-dose aspirin. However, 236 of them were excluded for the following reasons: 204 were prescribed NSAIDs, 23 had missing serum creatinine measurements, and 9 had basal kidney disease (nephritis, kidney cancer, and end-stage kidney disease requiring hemodialysis). Finally, 441 patients were included in this study. Patient characteristics classified on the basis of APAP exposure are shown in Table 1. The APAP exposure at \( >50 \, \text{g} \) was defined as CKD progression risk based on an APAP dose of 1.2 g, which is frequently used in Japan, and chronic administration for about 2 months or more. Also, short-term APAP use is not likely associated with CKD progression risk. Thus, we divided and analyzed three groups as follows: no APAP exposure, APAP exposure at 1–50 g, and APAP exposure at \( >50 \, \text{g} \). There were 277 patients in the non-concomitant APAP group, 138 patients in the APAP exposure at 1–50 g group, and 26 patients in the APAP exposure at \( >50 \, \text{g} \) group, respectively. Median APAP exposure was 8 g and 197 g in the APAP 1–50 g group and \( >50 \, \text{g} \) group, respectively. Although there were no significant differences among the three groups, the ratio of CKD progression tended to increase in the APAP \( >50 \, \text{g} \) group (\( p = 0.16 \)).

Patient characteristics classified on the basis of CKD progression are shown in Table 2. Age, hemoglobin A1c, frequency of DM, and frequency of ACE inhibitor use were significantly higher in the CKD progression group. Baseline CKD stage was also significantly different between both groups. Additionally, the CKD progression group tended to have a high ratio of APAP exposure at \( >50 \, \text{g} \) compared with the non-CKD progression group.

Factors associated with CKD progression based on multivariate analysis are shown in Table 3. APAP exposure \( >50 \, \text{g} \) (OR, 2.68, 95% CI, 1.08–6.70) had a positive association with CKD progression. Moreover, age increase by 1 year (OR, 1.05, 95% CI, 1.02–1.08) and DM (OR, 2.40, 95% CI, 1.41–4.08) had a positive association with CKD progression. In contrast, CKD stage 2 (OR, 0.25, 95% CI, 0.12–0.53) and 3 (OR, 0.09, 95% CI, 0.04–0.22) had a negative association with CKD progression.
DISCUSSION

Our results indicated that patients receiving low-dose aspirin were at increased risk of CKD progression through concomitant exposure to APAP. Although there is no data on the evaluation of the risk of CKD progression with concomitant APAP in patients taking low-dose aspirin, the risk of chronic renal failure was found to be increased among regular users of both aspirin and APAP compared with users of APAP alone.\(^5\) Moreover, daily use of analgesic mixtures that contain both aspirin and APAP produced renal papillary necrosis in female rats,\(^6\) and is associated with analgesic nephropathy in humans.\(^7\)

Although, a previous report suggested that aspirin in addition to $>500$ g APAP was associated with chronic renal failure,\(^3\) APAP $>50$ g as a lower dose was associated with CKD progression in this study. However, because the median daily prescription dose of APAP is $1.2$ g in Japan,\(^13\) it is expected that patients with APAP $>50$ g would have been exposed for more than about 2 months. Moreover, a median APAP exposure of $197$ g was close to a previous report of $>500$ g APAP. Moreover, because we assessed CKD progression risk and not renal failure, APAP $>50$ g may be a more sensitive indicator. Therefore, concomitant therapy with APAP and low-dose aspirin may be associated with an increased risk of CKD progression.

Aging and DM were also positively associated with CKD progression; however, these are already known risk factors for CKD progression.\(^{14,15}\) In contrast, CKD stage 2 and 3 were negatively associated with CKD progression. Although the risk of CKD progression is increased with advancing CKD stage in general, the amount of time required for CKD progression is longer in the elderly.\(^{16}\) This study included many elderly patients because we targeted all patients who received low-dose aspirin during the study period. Thus, while the reason for our conflicting results is

| Table 1. Patient Characteristics Classified on the Basis of APAP Exposure |
|-----------------------------|-----------------------------|-----------------------------|
|                             | 0 g ($N = 277$) | 1–50 g ($N = 138$) | $>50$ g ($N = 26$) |
| APAP exposure, g, median (range) | 0 (0) | 8 (0.4–47) | 197 (50–6340) |
| Sex male, $n$ (%) | 187 (68) | 93 (67) | 12 (46) |
| Age, years, median (range) | 69 (40–91) | 72 (37–92) | 79 (44–89) |
| BW, kg, median (range) | 61 (35–108) | 57 (30–102) | 50 (37–89) |
| CKD stage | 25 (9) | 17 (12) | 1 (4) |
| Hemoglobin A1c, median (range) | 5.7 (4.3–10.2) | 5.8 (4.3–12.3) | 5.7 (4.8–7.8) |
| Total cholesterol, mg/dL, median (range) | 181 (79–294) | 180 (100–287) | 178 (140–323) |
| Low-density lipoprotein, mg/dL, median (range) | 109 (29–203) | 105 (30–204) | 111 (47–207) |
| Basal disease, $n$ (%) | 75 (27) | 45 (33) | 5 (19) |
| Diabetic mellitus | 229 (83) | 111 (80) | 19 (73) |
| Medications | | | |
| Sulfonyl urea, $n$ (%) | 49 (18) | 33 (24) | 3 (12) |
| Biguanide, $n$ (%) | 26 (9) | 14 (10) | 1 (4) |
| Thiazolidine, $n$ (%) | 20 (7) | 12 (9) | 1 (4) |
| Dipeptidyl peptidase-4 inhibitor, $n$ (%) | 17 (6) | 8 (6) | 0 (0) |
| Calcium channel blocker, $n$ (%) | 151 (55) | 74 (54) | 11 (42) |
| ACE-I, $n$ (%) | 120 (43) | 51 (37) | 6 (23) |
| ARB, $n$ (%) | 63 (23) | 38 (28) | 9 (35) |
| Beta-blocker, $n$ (%) | 68 (25) | 29 (21) | 4 (15) |
| Statin, $n$ (%) | 146 (53) | 69 (50) | 13 (50) |
| CKD progression, $n$ (%) | 52 (19) | 28 (20) | 9 (35) |

APAP, acetaminophen; BW, body weight; CKD, chronic kidney disease; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.
Table 2. Patient Characteristics Classified on the Basis of CKD Progression

|                        | Non-CKD progression (N = 352) | CKD progression (N = 89) | p* |
|------------------------|-------------------------------|--------------------------|----|
| APAP exposure 0 g      | 225 (64)                     | 52 (58)                  |    |
| 1–50 g                | 110 (31)                     | 28 (32)                  | 0.16 |
| > 50 g                | 17 (5)                       | 9 (10)                   |    |
| Sex male, n (%)       | 231 (66)                     | 61 (69)                  | 0.71 |
| Age, years, median (range) | 70 (37–92)               | 73 (42–91)               | 0.04 |
| BW, kg, median (range) | 60 (30–102)                  | 58 (35–108)              | 0.31 |
| CKD stage 1           | 25 (7)                       | 18 (20)                  |    |
| 2                     | 204 (58)                     | 53 (60)                  |    |
| 3                     | 121 (34)                     | 17 (19)                  | <0.01 |
| 4                     | 2 (1)                        | 1 (1)                    |    |
| Hemoglobin A1c, median (range) | 5.7 (4.3–10.2)            | 5.9 (4.7–12.3)           | 0.03 |
| Total cholesterol, mg/dL, median (range) | 181 (79–294)         | 179 (118–323)            | 0.84 |
| Low-density lipoprotein, mg/dL, median (range) | 109 (29–204)         | 107 (46–207)             | 0.45 |
| Basal disease, n (%)  |                               |                          |    |
| Diabetes mellitus     | 90 (26)                      | 35 (39)                  | 0.01 |
| Hypertension          | 284 (81)                     | 75 (84)                  | 0.54 |
| Medications           |                               |                          |    |
| Sulfonyl urea, n (%)  | 63 (18)                      | 22 (25)                  | 0.18 |
| Biguanide, n (%)      | 31 (9)                       | 10 (11)                  | 0.54 |
| Thiazolidine, n (%)   | 23 (7)                       | 10 (11)                  | 0.17 |
| Dipeptidyl peptidase-4 inhibitor, n (%) | 19 (5)              | 6 (7)                    | 0.61 |
| Calcium channel blocker, n (%) | 182 (52)                | 54 (61)                  | 0.15 |
| ACE-I, n (%)          | 130 (37)                     | 47 (53)                  | <0.01 |
| ARB, n (%)            | 89 (25)                      | 21 (24)                  | 0.79 |
| Beta-blocker, n (%)   | 79 (22)                      | 22 (25)                  | 0.67 |
| Statin, n (%)         | 179 (51)                     | 49 (55)                  | 0.55 |

* Mann-Whitney U test or Fisher’s exact test. APAP, acetaminophen; BW, body weight; CKD, chronic kidney disease; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 3. Multivariate Logistic Regression Analyses of Factors Associated with CKD Progression

|                                               | OR     | 95% CI        | p*  |
|----------------------------------------------|--------|---------------|-----|
| Non-concomitant APAP exposure                 | 1.00   | [Reference]   |     |
| APAP 1–50 g                                  | 1.02   | 0.59–1.77     | 0.94|
| APAP > 50 g                                  | 2.68   | 1.08–6.70     | 0.03|
| CKD stage 1                                  | 1.00 [Reference] |               |     |
| 2                                            | 0.25   | 0.12–0.53     | <0.01|
| 3                                            | 0.09   | 0.04–0.22     | <0.01|
| 4                                            | 0.21   | 0.02–2.65     | 0.23|
| Age increase 1 year                          | 1.05   | 1.02–1.08     | <0.01|
| Non-diabetes mellitus                        | 1.00 [Reference] |               |     |
| Diabetes mellitus                            | 2.40   | 1.41–4.08     | <0.01|

* Multivariate logistic regression analyses. OR, odds ratio; CI, confidence interval; APAP, acetaminophen; CKD, chronic kidney disease; ACE-I, angiotensin-converting-enzyme inhibitor.

unclear, the inclusion of an elderly population may provide a clue.

Our study has some other limitations. It was a retrospective study with a small sample size, which may limit the generalizability of our results. In addition we did not assess adherence to APAP therapy or the use of over-the-counter APAP. However, in Japan, adherence to prescription drugs is high, and over-the-counter analgesic medications (e.g., APAP) are seldom used because of the Japanese universal healthcare system. Also, APAP could not be assessed in terms of the daily dose during the study period because the dose is usually changed in the clinical setting. Furthermore, clinicians may have been more likely to prescribe APAP rather than NSAIDs for patients with CKD; however, we excluded NSAID users, and evaluated differences between APAP users and non-users. In contrast, patients in pain who are prescribed APAP may have some comorbidities,
which may carry increased risk of CKD progression. Age, baseline CKD stage, and DM were identified as risk factors for CKD progression in multivariate modeling. Although possible confounders were adjusted for, warfarin and unknown confounders might have inadvertently been included in the multivariate modeling. Accordingly, more robust studies are needed to confirm our findings.

In conclusion, our findings suggest that concomitant therapy with APAP and low-dose aspirin increased the risk of CKD progression. Therefore, we recommend more thorough monitoring of serum creatinine for patients receiving concomitant therapy. Moreover, it is important to advise users of low-dose aspirin to avoid unnecessary concomitant use of APAP, in order to reduce the risk of CKD progression.

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Conflict of Interest The authors declare no conflict of interest.

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