**Introduction**

Routine analyses of alkaline phosphatase (AP) and \(\gamma\)-glutamyl transferase (\(\gamma\)-GT) levels are commonly performed in clinical settings because elevation of these enzymes is indicative of a wide range of diseases, including hepatobiliary and bone diseases. Serum AP levels alone are diagnostic for many renal diseases, including renal osteodystrophy, infarction, renal cell carcinoma, and renal allograft rejection [1-3]. Elevated serum AP levels may also be indicative of infection or inflammation involving the tubular interstitial cells in which these enzymes are abundant. Meanwhile, a significant increase in \(\gamma\)-GT activity was observed in cases of pyelonephritis, Alport's syndrome, Wilms' tumor, and glomerulonephritis [4]. However, despite the strong association between renal disease and elevated serum AP and \(\gamma\)-GT levels, a small subset of acute pyelonephritis patients exhibit ab-

**Serum alkaline phosphatase and \(\gamma\)-glutamyl transferase in acute pyelonephritis**

Chaehoon Han\(^1\), Young-Ki Lee\(^1\), Hayne Cho Park\(^1\), Ajin Cho\(^1\), Sun Ryoung Choi\(^1\), Jong-Woo Yoon\(^1\), Ja Ryong Koo\(^1\), Hyung Jik Kim\(^1\), Jung-Woo Noh\(^1\), Min-Jeong Park\(^2\)

\(^1\)Department of Internal Medicine, Hallym Kidney Research Institute, Hallym University College of Medicine, Seoul, Korea

\(^2\)Department of Laboratory Medicine, Hallym University College of Medicine, Seoul, Korea

**Background:** Elevated serum alkaline phosphatase (AP) and \(\gamma\)-glutamyl transferase (\(\gamma\)-GT) are commonly observed in patients with acute pyelonephritis. The goal of this study was to examine the clinical significance of elevated serum AP and \(\gamma\)-GT levels and to explore the mechanisms underlying these changes.

**Methods:** We examined serum AP and \(\gamma\)-GT levels in 438 patients with acute pyelonephritis. Urine AP/creatinine (Cr), urine \(\gamma\)-GT/Cr, fractional excretion of AP, and fractional excretion of \(\gamma\)-GT (FE\(_{\gamma\text{-GT}}\)) were evaluated in patients with elevated and normal serum levels. AP isoenzymes were also examined.

**Results:** We identified 77 patients (17.6%) with elevated serum AP and 134 patients (30.6%) with elevated serum \(\gamma\)-GT. Among them, both enzymes were elevated in 64 patients (14.6%). Older age, longer hospital stay, elevated baseline serum Cr, and complicated pyelonephritis were associated with increases in serum AP and \(\gamma\)-GT. Multivariate analysis showed that high serum AP levels were significantly correlated with renal impairment (odds ratio, 2.13; 95% confidence interval, 1.08-4.19; \(P = 0.029\)). FE\(_{\gamma\text{-GT}}\) was significantly lower in patients with elevated serum enzyme levels. The liver fraction for AP isoenzyme profile did not increase in patients with elevated serum AP.

**Conclusion:** Our results demonstrated that elevated serum AP and \(\gamma\)-GT levels are associated with complicated pyelonephritis and renal impairment. Lower FE\(_{\gamma\text{-GT}}\) levels in patients with elevated serum enzymes may be the result of decreased urinary excretion of these enzymes.

**Keywords:** Alkaline phosphatase, gamma-Glutamyltransferase, Pyelonephritis
normally high AP and/or γ-GT levels without conspicuous cause. A few studies have investigated the elevated enzyme phenomenon [3–5], but none has offered a possible mechanism. Herein, we investigated the clinical significance of serum AP and γ-GT in adult patients with acute pyelonephritis, and we examined possible underlying mechanisms.

Methods

Study population

Using a retrospective design, we enrolled patients who were admitted to Hallym University Kangnam Sacred Heart Hospital (Seoul, Korea) after presenting with acute pyelonephritis between March 2002 and February 2005. All study-related protocols were approved by the Institutional Review Board of Kangnam Sacred Heart Hospital (IRB No 2008-8-44). Acute pyelonephritis was diagnosed when all three of the following symptoms were present: 1) fever ≥ 38°C, 2) flank pain or costovertebral angle tenderness, and 3) pyuria on urinalysis (> 5 leukocytes per high-power field in spot urine specimens). Patients were excluded from the study if they met any of the following conditions: < 18 years old, received antibiotic treatment prior to admission, presence of any other infectious disease that could interfere with pyelonephritis diagnosis, clinical or laboratory evidence of liver or bone disease (hepatitis B or C virus carriers, alcohol abusers), pregnancy or lactation in women, malignant tumor history, or chronic kidney disease history. A total of 438 patients were included in our study.

Complicated pyelonephritis was defined as acute pyelonephritis with any of the following conditions [6]: diabetes mellitus or immunocompromised status; underlying functional or structural urologic abnormalities (such as neurogenic bladder, urolithiasis, urinary tract obstruction, congenital abnormalities, or reflux); an indwelling urinary catheter; emphysematous pyelonephritis; or renal or perirenal abscess formation.

Laboratory analyses

Serum samples were collected and measured for complete blood counts and biochemical analyses, including liver and renal function tests. Urine samples were collected from all patients on initial presentation and prior to antibiotic infusion. In all cases, abdomen ultrasonography or computed tomography was performed during the acute infection phase. For hospitalized patients, we prescribed ceftriaxone empirically until culture results were available. Antibiotic therapy duration ranged from 10 to 14 days. Patients were discharged when their clinical parameters improved (fever, nausea, vomiting, poor oral intake, or flank pain) and when they were able to tolerate oral antibiotics.

The estimated glomerular filtration rate (eGFR) was estimated according to the Modification of Diet in Renal Disease (MDRD) study equation: eGFR (mL/min/1.73 m²) = 175 × (serum Cr)⁻¹.154 × (Age)⁻⁰.²⁰⁰ × (0.742 if female) × (1.212 if African-American). Renal impairment was defined as baseline eGFR < 60 mL/min/1.73 m².

We measured AP activity using the p-nitrophenylphosphate method with diethanolamine buffers, and we evaluated γ-GT using the International Federation of Clinical Chemistry’s (IFCC) method [7]. Both AP and γ-GT activities were quantified using a Hitachi 747 auto analyzer (Tokyo, Japan). Abnormal AP levels were defined as > 237 IU/L. Abnormal γ-GT levels were defined as > 63 IU/L for males and > 35 IU/L for females. AP isoenzymes were separated by cellulose acetate membranes (Helena Laboratory, Beaumont, USA) and electrophoresed in a Tris-barbital-sodium buffer solution (ionic strength = 0.042).

Statistical analyses

Continuous data with a normal distribution were expressed as means ± standard deviations and compared by Student’s t test. Continuous data without a normal distribution were expressed as medians and interquartile ranges and compared using the Mann–Whitney U test. Differences in proportions were assessed using the chi-squared test. Pearson’s correlation coefficients were used to assess the linear relationship between enzymes and other measurements. The odds ratios (OR) and 95% confidence intervals (CI) of variables were estimated from multivariate logistic regression analyses. All statistical
analyses were performed using SPSS version 19.0 (IBM Co., Armonk, USA); P values < 0.05 were considered statistically significant.

Results

Subject demographics and clinical characteristics

Of the 438 patients enrolled in this study, 414 were female and 24 were male. The mean age was 45.9 ± 18.6 years (range, 18–93 years); basic characteristics and biochemical test results are summarized in Table 1. *Escherichia coli* was the most common pathogen (43.4% of all subjects; 86.4% of cases with positive microorganism culture) followed by *Klebsiella pneumoniae*. Ninety-one patients (20.8%) were diagnosed with complicated pyelonephritis (53 with diabetes, 29 with urolithiasis, 5 with neurogenic bladder, 3 with prostate disease, and 3 with congenital anomaly).

**Serum AP and \(\gamma\)-GT in acute pyelonephritis**

At the time of admission, the prevalences of high serum AP and \(\gamma\)-GT were 17.6% (77 cases) and 30.6% (134 cases), respectively. Both enzymes were elevated in 64 cases (14.6%).

Patients with high AP were significantly older than those with normal AP levels (54.4 ± 16.4 vs. 44.0 ± 18.5 years, \(P < 0.001\)) and they had longer hospital stays (9.7 ± 7.0 vs. 6.7 ± 5.1 days, \(P < 0.001\)); Table 2). The high AP group showed higher baseline serum Cr levels (1.25 ± 0.74 vs. 0.97 ± 0.68 mg/dL, \(P = 0.003\)), lower eGFR (62.2 ± 26.1 vs. 79.9 ± 24.2 mL/min/1.73 m\(^2\), \(P < 0.001\)), and exhibited a higher proportion of complicated pyelonephritis (31.2% vs. 18.6%, \(P = 0.020\)). Antibiotic sensitivity analyses demonstrated that ciprofloxacin susceptibility was 75.9% (165/218). There were no differences in AP levels between the patients with ciprofloxacin-resistant *E. coli* and those with ciprofloxacin-sensitive *E. coli* (162.0 [135.0–242.5] vs. 147.5 [121.3–209.25]). However, in

**Table 1. General patient characteristics (n = 438)**

| Variable          | Value                                      |
|-------------------|--------------------------------------------|
| Age (yr)          | 45.9 ± 18.6 (18–93)                       |
| Female gender     | 414 (94.5)                                 |
| Hospital days     | 7.2 ± 5.6                                  |
| WBC count (/μL)   | 11,607 ± 4,799                            |
| SCr (mg/dL)       | 1.02 ± 0.70                               |
| eGFR (mL/min/1.73 m\(^2\)) | 76.8 ± 25.4                              |
| AST (IU/L)        | 25.5 ± 26.2 (5–245)                       |
| ALT (IU/L)        | 26.3 ± 25.4 (5–559)                       |
| AP (IU/L)         | 185.3 ± 123.4 (62–1,423)                  |
| \(\gamma\)-GT (IU/L) | 45.0 ± 64.7 (4–509)                    |
| Complicated APN   | 91 (20.8)                                 |
| Positive urine culture | 218 (49.8)                              |

Data are presented mean ± standard deviation (range) or number (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; APN, acute pyelonephritis; eGFR, estimated glomerular filtration rate; \(\gamma\)-GT, gamma-glutamyl transferase; SCr, serum creatinine; WBC, white blood cell.

**Table 2. Comparison of the high and normal AP groups in acute pyelonephritis patients**

| Variable          | High serum AP (n = 77) | Normal serum AP (n = 361) | \(P\) value |
|-------------------|------------------------|---------------------------|-------------|
| Age (yr)          | 54.4 ± 16.4            | 44.0 ± 18.5               | < 0.001     |
| Sex, male         | 6 (7.8)                | 18 (5.0)                  | 0.404       |
| Hospital days     | 9.7 ± 7.0              | 6.7 ± 5.1                 | < 0.001     |
| Complicated APN   | 24 (31.2)              | 67 (18.6)                 | 0.020       |
| WBC count (/μL)   | 12,388 ± 6,174         | 11,440 ± 4,444            | 0.204       |
| SCr (mg/dL)       | 1.25 ± 0.74            | 0.97 ± 0.68               | 0.003       |
| eGFR (mL/min/1.73 m\(^2\)) | 62.2 ± 26.1           | 79.9 ± 24.2               | < 0.001     |
| Serum AST (IU/L)  | 30.0 (17.0–59.0)       | 17.0 (13.0–23.3)          | < 0.001     |
| Serum ALT (IU/L)  | 36.0 (20.0–70.0)       | 15.0 (11.0–23.0)          | < 0.001     |
| Serum AP (IU/L)   | 312.5 (263.5–414.0)    | 136.0 (114.0–168.0)       | < 0.001     |
| Serum \(\gamma\)-GT (IU/L) | 97.0 (43.8–196.0)     | 18.0 (12.0–29.0)          | < 0.001     |

Data are presented as mean ± standard deviation, number (%), or median (range).

High serum AP levels were defined as > 237 IU/L.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; APN, acute pyelonephritis; eGFR, estimated glomerular filtration rate; \(\gamma\)-GT, gamma-glutamyl transferase; SCr, serum creatinine; WBC, white blood cell.
most patients, AP values returned to normal levels within 2 weeks (75.9%) as patients responded to antibiotic therapy.

Patients in the high $\gamma$-GT group were significantly older than those in the normal $\gamma$-GT group ($P < 0.001$) and had longer hospital stays (8.1 ± 5.4 vs. 6.8 ± 5.6 days, $P = 0.04$; Table 3). The high $\gamma$-GT group showed higher baseline serum Cr levels (1.19 ± 1.05 vs. 0.94 ± 0.45 mg/dL, $P = 0.009$) and lower eGFR (68.4 ± 26.6 vs. 80.5 ± 24.0 mL/min/1.73 m$^2$, $P < 0.001$). There was no significant difference in the proportion of complicated pyelonephritis between the groups. There were no differences in $\gamma$-GT levels between the patients with ciprofloxacin-resistant E. coli (24.5 [18.0–71.0] vs. 21.0 [13.0–21.5]). In 67.4% of the high $\gamma$-GT group, antibiotic treatment resulted in reduction of serum $\gamma$-GT to normal levels within 2 weeks of initiating treatment.

Hospital-stay duration had a significant positive correlation with both AP ($r = 0.29$, $P < 0.001$) and $\gamma$-GT ($r = 0.14$, $P = 0.003$) levels. Serum AP was also positively correlated with age ($r = 0.26$, $P < 0.001$), serum Cr ($r = 0.14$, $P = 0.005$), aspartate aminotransferase (AST; $r = 0.40$, $P < 0.001$), alanine aminotransferase (ALT; $r = 0.43$, $P < 0.001$), and $\gamma$-GT ($r = 0.67$, $P < 0.001$). Serum $\gamma$-GT was positively correlated with age ($r = 0.14$, $P = 0.003$), serum Cr ($r = 0.16$, $P = 0.001$), AST ($r = 0.51$, $P < 0.001$), and ALT ($r = 0.54$, $P < 0.001$). Multivariate regression analyses showed that high serum AP levels (OR, 2.47; 95% CI, 1.26–7.84; $P = 0.008$) were significantly correlated with longer hospital stays (> 7 days).

### Table 3. Comparison of the high and normal $\gamma$-GT groups in acute pyelonephritis patients

| Variable               | High serum $\gamma$-GT (n = 134) | Normal serum $\gamma$-GT (n = 304) | $P$ value |
|------------------------|----------------------------------|-------------------------------------|-----------|
| Age (yr)               | 51.1 ± 15.6                      | 43.6 ± 19.3                         | < 0.001   |
| Sex, male              | 9 (6.7)                          | 15 (4.9)                            | 0.496     |
| Hospital days          | 8.1 ± 5.4                        | 6.8 ± 5.6                           | 0.029     |
| Complicated APN        | 27 (20.1)                        | 64 (21.1)                           | 0.899     |
| WBC count (/μL)        | 11,482 ± 4,863                   | 11,662 ± 4,778                      | 0.718     |
| SCr (mg/dL)            | 1.19 ± 1.05                      | 0.94 ± 0.45                         | 0.009     |
| eGFR (mL/min/1.73 m$^2$)| 68.4 ± 26.6                      | 80.5 ± 24.0                         | < 0.001   |
| Serum AST (IU/L)       | 28.0 (18.0–43.0)                 | 16.0 (13.0–21.0)                    | < 0.001   |
| Serum ALT (IU/L)       | 31.5 (20.0–52.3)                 | 14.0 (10.8–19.3)                    | < 0.001   |
| Serum AP (IU/L)        | 230.0 (159.0–325.8)              | 132.0 (112.8–165.3)                 | < 0.001   |
| Serum $\gamma$-GT (IU/L)| 73.5 (50.8–129.8)               | 15.5 (11.0–21.0)                    | < 0.001   |

Data are presented as mean ± standard deviation, number (%), or median (range).
High serum $\gamma$-GT levels were defined as >63 IU/L for males, and >35 IU/L for females.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; APN, acute pyelonephritis; eGFR, estimated glomerular filtration rate; $\gamma$-GT, gamma-glutamyl transferase; SCr, serum creatinine; WBC, white blood cell.

### Table 4. Independent factors associated with long hospital stays in acute pyelonephritis patients

| Variable               | Univariate OR (95% CI) | Univariate $P$ value | Multivariate OR (95% CI) | Multivariate $P$ value |
|------------------------|------------------------|----------------------|--------------------------|------------------------|
| Age (yr)               | 1.032 (1.020–1.044)    | < 0.001              | 1.016 (1.002–1.030)      | 0.029                  |
| Sex, male              | 2.981 (1.299–6.839)    | 0.010                | 2.193 (0.859–5.594)      | 0.100                  |
| Diabetes mellitus      | 4.139 (2.291–7.476)    | < 0.001              | 2.399 (1.204–4.872)      | 0.013                  |
| SCr (mg/dL)            | 10.739 (4.609–25.022)  | < 0.001              | 4.247 (1.860–9.695)      | 0.001                  |
| High serum AP          | 4.990 (2.972–8.375)    | < 0.001              | 2.469 (1.260–4.838)      | 0.008                  |
| High serum $\gamma$-GT | 2.920 (1.872–4.554)    | < 0.001              | 1.550 (0.856–2.808)      | 0.148                  |
| High serum AST         | 1.459 (0.792–2.687)    | 0.225                |                          |                        |
| High serum ALT         | 1.401 (0.740–2.654)    | 0.301                |                          |                        |

High serum AP levels were defined as > 237 IU/L. High $\gamma$-GT levels were defined as > 63 IU/L for males, and > 35 IU/L for females. High AST/ALT levels were defined as > 45 IU/L.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; OR, odds ratio; $\gamma$-GT, gamma-glutamyl transferase; SCr, serum creatinine.
7 days). The results also showed that serum Cr, diabetes mellitus, and age were independent risk factors for longer hospital stays (Table 4).

Our data also demonstrated a significant association of eGFR with both AP ($r = -0.26$, $P < 0.001$) and $\gamma$-GT ($r = -0.214$, $P < 0.001$). Multivariate analyses showed that high serum AP levels, not $\gamma$-GT, were significantly correlated with renal impairment (OR, 2.13; 95% CI, 1.08–4.19; $P = 0.029$). The results also showed that age and diabetes mellitus were independent risk factors associated with renal impairment (Table 5).

Area under the curve (AUC) of the receiver operator characteristic (ROC) plot analysis was used to assess diagnostic and prognostic enzyme performance. ROC plot analysis showed that serum AP and $\gamma$-GT had significant discriminating power for long hospital stays (AUC, 0.635; 95% CI, 0.573–0.698; $P < 0.001$ and AUC, 0.619; 95% CI, 0.557–0.680, $P = 0.001$; respectively). Serum AP and $\gamma$-GT also had discriminating power for renal impairment (AUC, 0.611; 95% CI, 0.546–0.676; $P = 0.001$ and AUC, 0.595; 95% CI, 0.532–0.659; $P = 0.003$; respectively).

### Fractional excretion and isoenzyme analysis

We evaluated urine AP/Cr, urine $\gamma$-GT/Cr, FE_{AP}, and FE_{GT} in patients with elevated (n = 20, group A) and normal (n = 17, group B) serum AP and $\gamma$-GT levels. No significant differences were observed for urine AP/Cr, $\gamma$-GT/Cr, or FE_{AP} between the groups (Table 6). Urine $\gamma$-GT/Cr and FE_{AP} were marginally significantly lower in the elevated enzyme group compared with the normal enzyme group ($P = 0.088$ and 0.082). Average FE_{GT} was significantly lower in the elevated enzyme group compared with the normal group ($P < 0.001$).

### Discussion

AP is present in most human tissues, including liver, bone, intestine, placenta, kidney, and white blood cells [8,9]. Within the kidney, AP activity is highest in the proximal convoluted tubules [8] with average activity levels 2.1-fold higher than in the distal convoluted tubules, and

### Table 6. Urine levels and fractional excretion of AP (FE_{AP}) and $\gamma$-GT (FE_{GT})

| Variable | Group A (n = 20) | Group B (n = 17) | P value |
|----------|-----------------|-----------------|---------|
| Urine AP/Cr (IU/mg) | 0.28 (0.11–0.51) | 0.19 (0.12–0.69) | 0.446 |
| Urine $\gamma$-GT/Cr (IU/mg) | 0.53 (0.24–0.62) | 0.74 (0.49–0.89) | 0.088 |
| FE_{AP} | 0.09 (0.04–0.13) | 0.12 (0.07–0.36) | 0.082 |
| FE_{GT} | 0.43 (0.26–0.89) | 3.40 (2.16–4.78) | < 0.001 |

Group A was defined as patients with elevated serum AP ($> 237$ IU/L) and $\gamma$-GT ($> 63$ IU/L for males and $> 35$ IU/L for females). Group B was defined as normal serum AP ($< 237$ IU/L) and $\gamma$-GT ($< 63$ IU/L for males and $< 35$ IU/L for females).

AP, alkaline phosphatase; Cr, creatinine; FE, fractional excretion; $\gamma$-GT, gamma-glutamyl transferase.
4.7-fold higher than in the renal papilla. Because acute pyelonephritis usually involves both the renal pelvis and parenchyma, serum AP is likely to be significantly elevated in some acute pyelonephritis patients, making AP a promising indicator of severe renal parenchymal damage. A few studies have identified an association between elevated serum AP and acute pyelonephritis. Refaie et al [3] observed a 2.2-fold increase in serum AP levels in patients with acute pyelonephritis relative to controls, while another retrospective study identified a subset of acute pyelonephritis patients (14.7%) with significantly elevated serum AP [5].

Furthermore, a few studies have reported possible links between serum γ-GT and acute pyelonephritis. While γ-GT is present in a variety of tissues, including liver, pancreas, spleen, lung, small intestine, and placenta [10], the highest γ-GT concentrations are found in the brush border of the proximal tubules and the loop of Henle [11], suggesting an association with renal function. In our study, 17.6% of acute pyelonephritis patients exhibited elevated serum AP while 30.6% had elevated serum γ-GT; in 14.6%, both enzymes were elevated.

Our results showed a significant correlation between elevated serum AP and hospital-stay duration. Elevated serum AP was also modestly associated with age, serum Cr, and complicated pyelonephritis. These findings suggest a functional link between acute pyelonephritis severity and serum AP level. A previous study by Fotino [5] suggested that acute pyelonephritis may be attributable to elevated serum AP based on evidence of extensive parenchymal destruction in study patients' kidneys. Along with serum AP, we observed strong correlations between elevated serum γ-GT and hospital-stay duration, old age, and serum Cr in the subset of acute pyelonephritis patients. However, multivariate regression analyses showed that high serum γ-GT was not an independent risk factor for long hospital stays.

Likewise, serum AP, but not serum γ-GT, was useful for discriminating patients with renal impairment. A high degree of enzyme activity in the kidneys makes urinary tubular enzymes an excellent diagnostic tool for predicting acute kidney injury (AKI) [12,13] 12 hours to 4 days earlier than serum Cr [13]. There are four major categories of AKI biomarkers: functional markers (serum cystatin-C), up-regulated proteins (NGAL, KIM-1, L-FABP, and IL-18), low-molecular weight proteins (urine cystatin-C), and enzymes (N-acetyl-β-D-glucosaminidase, AP, and γ-GT) [15]. There are relatively few clinical studies of enzyme biomarkers, but Westhuyzen et al [14] reported that AP (AUC, 0.863) and γ-GT (AUC, 0.950) had excellent discriminating power for AKI. However, the AKI predictive power was low for either AP/urine Cr or γ-GT/urine Cr; both yielded AUCs < 0.7 [16]. Our study demonstrated an association between serum enzymes and concurrent renal impairment. However, we did not evaluate the effect of elevated enzymes upon sustained renal function decline or mortality, for which further research is warranted.

Next, we examined whether elevated serum enzymes were the result of increased enzyme release by inflammatory renal damage, decreased renal excretion, or nonspecific liver damage. Although FEγ-GT was the only factor exhibiting a significant decrease in the high serum enzyme group, other factors, such as urine AP/Cr, γ-GT/Cr, and FEap, were lower in the high serum enzyme group compared with normal controls. These results suggest that serum enzyme elevation can be attributed, in part, to decreased renal excretion, which likely stems from an increase in renal absorption of these enzymes.

An alternative explanation for elevated serum enzymes may be the release of enzymes originating from outside the kidneys, with the most likely source being the liver. Severe sepsis and hypotension result in nonspecific liver damage, which may result in the release of AP and γ-GT into circulation. However, liver fraction of AP isoenzyme was not elevated in acute pyelonephritis patients, suggesting that the liver is not the source of increased serum enzymes. Furthermore, complete normalization of AP and/or γ-GT levels in most acute pyelonephritis cases provides additional evidence that elevated AP and/or γ-GT levels are directly associated with acute pyelonephritis.

Our study has several limitations. First, we did not evaluate biomarkers such as cystatin C, NGAL, or KIM-1. Second, our sample size for fractional excretion and isoenzyme analyses was small. However, our data demonstrated that high AP and γ-GT levels were associated with complicated pyelonephritis and renal impairment. We also conclude that decreased renal enzyme excretion is a cause of high serum levels in acute pyelonephritis patients. A few studies have investigated the phenomenon of enzyme elevation [3–5], but no study has proposed an
underlying mechanism. Ours is the first study to suggest a possible mechanism for enzyme elevation in acute pyelonephritis patients.

In conclusion, our results demonstrated that serum AP and γ-GT levels are significantly elevated in a subset of acute pyelonephritis patients. Furthermore, lower urine AP/Cr, urine γ-GT/Cr, FE AP, and FE γ-GT levels combined with high serum enzymes in acute pyelonephritis patients suggest a causal link between diminished urinary excretion and elevated serum concentrations of these enzymes. A final analysis of AP isoenzyme profiles demonstrated that extra renal organs, including the liver, were unlikely to be the origin of serum AP elevation in acute pyelonephritis patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Chaehoon Han, Hayne Cho Park, and Sun Ryoung Choi participated in the data collection and wrote the manuscript. Ja Ryong Koo, Hyung Jik Kim, and Jung-Woo Noh participated in the study design and performed the statistical analysis. Min-Jeong Park participated in the conception, biochemical analysis, and interpretation of data. Jong-Woo Yoon and Ajin Cho provided intellectual content of critical importance to the work and technical support. Young-Ki Lee participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

References

[1] Gault MH, Steiner G. Serum and urinary enzyme activity after renal infarction. Can Med Assoc J 1965;93:1101-1105.
[2] Atlas I, Kwan D, Stone N. Value of serum alkaline phosphatase and radionuclide bone scans in patients with renal cell carcinoma. Urology 1991;38:220-222.
[3] Refaei MO, Abo-Zaid H, Gomma NA, Aboul-Enein HY. Determination of urinary and serum beta-glucuronidase and alkaline phosphatase in various renal disease and kidney rejection transplanted patients. Prep Biochem Biotechnol 2000;30:93-106.
[4] Salgó L, Szabó A. Gamma-glutamyl transpeptidase activity in human urine. Clin Chim Acta 1982;126:9-16.
[5] Fotino S. Elevation of serum alkaline phosphatase in severe pyelonephritis and obstructive nephropathy. Nephron 1974;12:197-210.
[6] Bergeron MG. Treatment of pyelonephritis in adults. Med Clin North Am 1995;79:619-649.
[7] Shaw LM, Strømme JH, London JL, Theodorsen L. International Federation of Clinical Chemistry. Scientific Committee, Analytical Section. Expert Panel on Enzymes. IFCC methods for measurement of enzymes. Part 4. IFCC methods for gamma-glutamyltransferase [(gamma-glutamyl)-peptide: amino acid gamma-glutamyltransferase, EC 2.3.2.2]. IFCC Document, Stage 2, Draft 2, 1983-01 with a view to an IFCC Recommendation. Clin Chim Acta 1983;135:315F-338F.
[8] Bonting SL, Pollak VE, Muehrcke RC, Kark RM. Quantitative histochemistry of the nephron. III. Lactic dehydrogenase activity in man and other species. J Clin Invest 1960;39:1381-1385.
[9] Kaplan MM. Alkaline phosphatase. N Engl J Med 1972;286:200-202.
[10] Zein M, Discombe G. Serum gamma-glutamyl transpeptidase as a diagnostic aid. Lancet 1970;2:748-750.
[11] Albert Z, Orlowski M, Szewczuk A. Histochemical demonstration of gamma-glutamyl transpeptidase. Nature 1961;191:767-768.
[12] Trof RJ, Di Maggio F, Leemreis J, Groeneveld AB. Biomarkers of acute renal injury and renal failure. Shock 2006;26:245-253.
[13] Scherberich JE. Urinary proteins of tubular origin: basic immunochemical and clinical aspects. Am J Nephrol 1990;10 Suppl 1:43-51.
[14] Westhuyzen J, Endre ZH, Reece G, Reith DM, Saltissi D, Morgan TJ. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 2003;18:543-551.
[15] de Geus HR, Betjes MG, Bakker J. Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges. Clin Kidney J 2012;5:102-108.
[16] Endre ZH, Pickering JW, Walker RJ, et al. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney Int 2011;79:1119-1130.