Analysis of Factors Causing Hyperkalemia

Kenmei Takaichi¹, Fumi Takemoto¹, Yoshifumi Ubara¹ and Yasumichi Mori²

Abstract

Objective  Patients with impaired renal function or diabetes are considered to be prone to hyperkalemia. Furthermore, hyperkalemia is an adverse drug reaction of inhibitors of the renin-angiotensin system (RAS) that are established to be efficacious in these patients. However, the current status of hyperkalemia in the clinical setting remains obscure.

Methods  A total of 9,117 patients treated at Toranomon Hospital between January and October 2005, who had serum creatinine levels below 5 mg/dL were studied. Patients on dialysis and patients using cation exchange resin or diuretics that lower serum potassium were excluded.

Results  Serum potassium increased significantly accompanying the increase in serum creatinine, and was significantly elevated in diabetic patients compared to non-diabetic patients. Serum potassium also increased significantly with the administration of angiotensin-II receptor blockers (ARB), angiotensin-converting-enzyme inhibitors (ACEI) or beta-blockers. A combination of diabetes and RAS inhibitor administration significantly increased serum potassium compared to each factor alone in patients with a serum creatinine level below 1.5 mg/dL but not in those with a higher serum creatinine level. According to step-wise multiple regression analyses, an elevated serum creatinine level had the strongest positive correlation with the serum potassium level, followed by diabetes, ACEI use, ARB use, and age.

Conclusion  Lowered renal function, diabetes, use of RAS inhibitors and old age are independent factors that increase the serum potassium level. Caution should be exercised when using RAS inhibitors in diabetic patients even if their renal function is relatively preserved. In selected patients with diabetes or impaired renal function, however, RAS inhibitors can be used without hyperkalemia.

Key words: diabetes, hyperkalemia, angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers, age, renal function

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Introduction

Inhibitors of the renin-angiotensin system (RAS) are widely used clinically for their beneficial effects of preserving cardiac function (1, 2), and also for conserving renal function (3). Several large-scale trials have verified that angiotensin-converting-enzyme inhibitors (ACEI) suppress the progression of renal function deterioration in type 1 diabetes (4), and that angiotensin-II receptor blockers (ARB) prevent the aggravation of renal function in type 2 diabetes (5-7). Currently, RAS inhibitors are one of the most widely used antihypertensive agents in diabetic patients. On the other hand, hyperkalemia is a well recognized adverse drug reaction of RAS inhibitors. Further, hyperkalemia is known to occur at higher rates in patients with lowered renal function or diabetes (8, 9). Apart from RAS inhibitors, other agents such as beta-blockers are also well known to increase serum potassium levels (10). Despite such awareness, many nephrologists and diabetologists in the clinical setting are using RAS inhibitors for their renoprotective effect even in patients with lowered renal function or diabetes, while monitoring these patients to prevent hyperkalemia.

The objective of the present study was to investigate whether hyperkalemia occurs in patients who are under clinical management. A total of 9,117 patients managed by the departments of nephrology and diabetes at the Toranomon Hospital were studied to analyze the factors causing hyperkalemia. Toranomon Hospital has been accredited as a training facility by the Japanese Society of Nephrology and

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the Japan Diabetes Society. The results of analyses identified lowered renal function, diabetes, use of RAS inhibitors, and age as independent risk factors of hyperkalemia. In addition, the results also clearly showed that in patients with relatively preserved renal function (serum creatinine lower than 1.5 mg/dL), although the mean serum potassium level is within the normal range, the serum potassium level increases significantly when concurrent diabetes and RAS inhibitor use overlap. On the other hand, even in patients with a serum creatinine level of 2 mg/dL or above, RAS inhibitors can be used in selected patients regardless of their diabetes status.

### Patients and Methods

All patients treated at the Departments of Nephrology and Diabetes of Toranomon Hospital between January to end of October 2005, who had serum creatinine levels lower than 5 mg/dL and well documented prescribed medications were enrolled. A total of 9,117 patients with 38,181 measurements were studied retrospectively, after excluding patients on dialysis and patients using cation exchange resin or diuretics that lower the serum potassium level. For patients who had multiple sets of blood test results during the study period, the dataset with the highest serum potassium level was used for the analysis of factors causing hyperkalemia. In the analysis of the effects of drugs, the drugs used at the time of obtaining the dataset were examined. The investigation items were age, gender, serum potassium level, serum creatinine level, spot blood glucose level, fasting blood glucose level, and HbA1c level. In addition, the prescription status during the study period was investigated. Diabetes was defined as a spot blood glucose level of 200 mg/dL or above, a fasting blood glucose of 126 mg/dL or above, or a HbA1c level of 6.5% or above during the study period.

This study was approved by the Toranomon Hospital Institutional Review Board of Clinical Research and the need for informed consent from the patients was waived because of its retrospective design.

### Statistical analysis

To analyze the relationship between the serum potassium level and renal function, an additional analysis was conducted after stratifying based on serum creatinine levels <1.0 mg/dL, ≥1.0 and <1.5 mg/dL, ≥1.5 and <2.0 mg/dL, ≥2.0 and <3.0 mg/dL, as well as ≥3.0 and <5.0 mg/dL. Analysis was also conducted after stratifying by age groups of <30 years, ≥30 and <40 years, ≥40 and <50 years, ≥50 and <60 years, ≥60 and <70 years, ≥70 and <80 years, as well as ≥80 years.

Data are expressed in mean±standard error. Serum potassium levels were analyzed statistically by analysis of variance and Scheffe’s multiple comparison. The relations between serum potassium level and other factors were examined by step-wise multiple regression analysis using serum potassium level as the dependent variable. The significance level was set at 5% (two-sided). Statistical analyses were conducted using SAS.

### Results

#### 1. Patient background

The background of 9,117 patients is shown in Table 1. The mean age was 60.0±0.1 years. Males occupied 57.7% of the patients, and 39.6% had diabetes concurrently.

#### 2. Relation between renal function and serum potassium level

The relation between serum creatinine level and serum potassium level is shown in Fig. 1. The serum potassium level increased significantly accompanying the increase in serum creatinine level (ANOVA: p<0.001).

#### 3. Serum potassium level according to the presence or absence of diabetes

The mean serum potassium level was 4.56±0.006 mEq/L in diabetic patients and was significantly higher (p<0.001) than the level of 4.40±0.005 mEq/L in non-diabetic patients, showing elevated serum potassium levels in the presence of diabetes.
Figure 1. Relation between serum potassium levels (mEq/L) and renal function.

Figure 2. Differences in serum potassium levels between diabetic and non-diabetic patient.

The distribution of serum creatinine levels and serum potassium levels in diabetic and non-diabetic patients is shown in Fig. 2. Elevation of the serum potassium level accompanying the increase in the serum creatinine level was observed regardless of the status of diabetes. In a comparison of the two regression lines, there was a shift toward higher serum potassium levels in diabetic patients.

Serum potassium levels stratified by serum creatinine levels are shown in Fig. 3. At serum creatinine levels below 2 mg/dL, a significant (p<0.01) increase in the serum potassium level was observed in the group with diabetes. In contrast, at serum creatinine levels of 2 mg/dL and above, no significant change in the serum potassium level was observed with and without diabetes. While patients with a serum creatinine level below 2.0 mg/dL had mean serum potassium levels of lower than 5 mEq/L, an unnegligible proportion of patients (4% in non-diabetic and 10% in diabetic patients) with serum potassium levels above normal (5.0 mEq/L or higher) was present even among patients with a low serum creatinine level.

4. Relation between the serum potassium level and drugs potentially elevating serum potassium level

The relation between the serum potassium level and ad-
Figure 3. Serum potassium levels (mEq/L) stratified by serum creatinine levels in diabetic and non-diabetic patients.

Table 2. Relations between Serum Potassium Levels and Drugs Potentially Increasing potassium. ACEI: angiotensin-converting-enzyme inhibitors, ARB: angiotensin-II receptor blockers, RAS: renin-angiotensin system.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number</th>
<th>Serum Potassium (mEq/L)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No blockade of RAS</td>
<td>7988</td>
<td>4.45 ± 0.004</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>With ACEI</td>
<td>357</td>
<td>4.59 ± 0.021</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No blockade of RAS</td>
<td>7988</td>
<td>4.45 ± 0.004</td>
<td></td>
</tr>
<tr>
<td>With ARB</td>
<td>831</td>
<td>4.58 ± 0.013</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Without beta-blockers</td>
<td>8874</td>
<td>4.46 ± 0.004</td>
<td></td>
</tr>
<tr>
<td>With beta-blockers</td>
<td>243</td>
<td>4.56 ± 0.023</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Mean ± S.E.

ministration of drugs that potentially increase serum potassium level is shown in Table 2. The serum potassium level increased significantly (p<0.001) by the administration of ARB, ACEI and beta-blockers. The relationships between serum creatinine and serum potassium levels according to the prescribed drug class are shown in Fig. 4. For all three drug classes, the serum potassium level increased significantly when the serum creatinine level was low. Significant differences were observed when serum creatinine levels were below 1.0 mg/dL (p<0.001), below 1.5 mg/dL (p<0.001), and below 2.0 mg/dL (p<0.01) in patients administered ACEI; when serum creatinine levels were below 1.0 mg/dL (p<0.001) and below 1.5 mg/dL (p<0.01) in patients administered ARB; and when serum creatinine level was below 1.0 mg/dL (p<0.05) in patients administered beta-blockers.

5. Effect of the combination of diabetes and RAS inhibitor prescription on serum potassium level

Since diabetes and RAS inhibitor prescription individually were proven to increase the serum potassium level, the effect of a combination of these two factors was examined (Fig. 5). For both ACEI and ARB, among patients with a serum creatinine level below 1.5 mg/dL, the serum potassium level increased in the presence of diabetes or drug administration compared to no diabetes and no drug administration, and was significantly increased with a combination of diabetes and RAS inhibitor administration. Of 8,743 patients with a serum creatinine level below 1.5 mg/dL, 541 had serum potassium levels above normal (5.0 mEq/L or above). Among them, 165 patients had no diabetes and received no ACEI or ARB, and the remaining 376 patients (70%) had diabetes or were receiving AECI or ARB.

In patients with a serum creatinine level of 1.5 mg/dL and above, although the serum potassium levels were high overall, no significant differences were observed between the four groups (Fig. 5). The large variation observed in patients given ACEI was probably caused by the small number of patients.
6. Relation between serum potassium level and age or gender

The relation between age and serum potassium level is shown in Fig. 6. A mild but significant age-related increase in serum potassium level was observed. As for the relation between gender and serum potassium level, the mean serum potassium levels were 4.51±0.005 in males and 4.40±0.006 in females, and was significantly (p<0.001) higher in males.

7. Relation between serum potassium level and various factors

Step-wise multiple regression analysis was conducted using serum creatinine level, diabetes status, ARB use, ACEI use, beta-blocker use, age and gender as independent variables to examine the effects of the above-mentioned factors on serum potassium level. As shown in Table 3, an elevated serum creatinine had the strongest positive correlation, followed in descending order by diabetes, ACEI use, ARB use and age, all of which showed a significant correlation. No significant relation was observed with gender and beta-blocker use.

Discussion

In the human body, potassium present in extracellular fluid constitutes approximately 2% of the total potassium. In healthy adults, the serum potassium level is strictly controlled within the narrow range of 3.5 to 5.0 mEq/L, irrespective of the dietary potassium intake. This is achieved by maintaining the balance between the amount of intake and amount excreted via the kidney and intestinal tract, and the balance between intracellular and extracellular concentrations. Renal elimination is the main excretion route of potas-
sium, and approximately 90% is excreted via the kidneys. Therefore lowered renal function predisposes hyperkalemia.

Hyperkalemia affects the excitation conduction system of the heart. Further increase of blood potassium is associated with risks of severe arrhythmia. Moreover, the effect on the excitation conduction system does not always parallel the serum potassium level, and individual variation is said to be great. Therefore, controlling serum potassium level within a safe range is of great importance. In addition to lowered renal function, diabetes is a well known condition that increases the risk of hyperkalemia. Extracellular potassium is taken up intracellularly by insulin action. In diabetes in which the insulin action is insufficient or deficient, the serum potassium level increases (11, 12).

While fully aware of the fact that lowered renal function and diabetes are risk factors of hyperkalemia, many nephrologists and diabetologists continue to use RAS inhibitors at high frequencies, expecting to benefit from their renoprotective effect. In the present study, serum potassium level increased accompanying an increase in serum creatinine level, confirming lowered renal function as an important factor of hyperkalemia. In addition, our study also demonstrated that the presence of diabetes increases serum potassium level. Paradoxically, analysis after stratifying according to serum creatinine level showed a significant increase in the serum potassium level associated with diabetes only when the serum creatinine level was below 2 mg/dL. Moreover, ACEI or ARB administration also increased the serum potassium level in patients with a low serum creatinine level, similar to diabetes. Furthermore, the effect of a combination of diabetes and ACEI or ARB administration was also evident. In patients with a serum creatinine level below 1.5 mg/dL, the presence of diabetes together with ACEI or ARB administration was associated with a significant increase in the serum potassium level, and among patients with serum potassium levels exceeding the normal range (5.0 mEq/L or above), 70% of them either had diabetes or were receiving ACEI or ARB. On the other hand, in patients with a serum creatinine level of 1.5 mg/dL and above, although the serum potassium levels were high overall, no differences were observed between the four groups.

It should be stressed that these results do not imply that

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**Figure 6.** Serum potassium levels (mEq/L) stratified by age.

**Table 3.** Multiple Regression Analysis. ACEI: Angiotensin-converting-enzyme Inhibitors, ARB: Angiotensin-II Receptor Blockers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Partial regression coefficient</th>
<th>Standard partial regression coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum creatinine</td>
<td>0.299004</td>
<td>0.315328</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>diabetes</td>
<td>0.145823</td>
<td>0.195691</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACEI administration</td>
<td>0.056914</td>
<td>0.030294</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ARB administration</td>
<td>0.048491</td>
<td>0.038661</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>age</td>
<td>0.003528</td>
<td>0.134145</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

stepwise forward selection method: \( \geq F \text{ in } 2 \), \( < F \text{ out } 2 \)

multiple coefficient of determination \( R^2 = 0.182664 \)

multiple correlation coefficient \( R = 0.427392 \)
diabetes and RAS inhibitors do not increase the serum potassium level in patients with a high serum creatinine level. In this study, analyses were conducted after excluding patients who were using cation exchange resin that adsorbs potassium and patients who were using diuretics that promote potassium excretion and are used frequently by patients with renal dysfunction, because these agents interfere with the serum potassium level. In actual fact, the frequency of the patients prescribed potassium-absorbing cation exchange resin and potassium-excreting diuretics was increased in accordance with the increase in serum creatinine level. The ratios of the patients using potassium-absorbing cation exchange resin or potassium-excreting diuretics in the patients with serum creatinine level less than 1.5 mg/dL were 0.1% and 1.7%, respectively, and the ratios in those with a higher serum creatinine level were 6.1% and 10.9%, respectively. It is also very possible that RAS inhibitors were used in the patients with decreased renal function only if they had a normal potassium level or they could restrict potassium intake. The important point of the present study is that diabetes and RAS inhibitors increase the serum potassium level mildly but significantly in patients with a relatively low serum creatinine level. It also possible that some patients with decreased renal function are included in those with a low serum creatinine level, because serum creatinine level depends on muscle mass as well as on renal function. Therefore, caution has to be exercised when using RAS inhibitors even in patients with a relatively low serum creatinine level. On the other hand, even in patients with renal dysfunction, RAS inhibitors can be used in selected patients, without supplementing cation exchange resin or diuretics to control the potassium level.

As for individual factors, serum creatinine level, diabetes, use of ACEI or ARB, use of beta-blockers, old age and the male gender were found to potentially increase serum potassium. Since these factors may be mutually related, we conducted step-wise multiple regression analysis to verify the effects of these factors on serum potassium. The result of analysis revealed that the serum creatinine level and diabetes are the most important independent factors for increasing serum potassium. Moreover, while use of ACEI or ARB and old age were also identified as factors that increase serum potassium level, use of beta-blockers and gender were found to be not significantly related.

In summary, patients with lowered renal function, diabetic patients, patients using RAS inhibitors, and elderly patients are independent factors that increase the serum potassium level. Therefore, caution should be exercised when using RAS inhibitors in patients with lowered renal function, diabetic patients and elderly patients. In addition, even though renal function is only mildly impaired, RAS inhibitors increase the serum potassium level and therefore should be used with care in individual patients. On the other hand, even in patients with more advanced renal dysfunction, RAS inhibitors can be used in some patients without supplementing cation exchange resin or diuretics for potassium control.

References


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