Angiotensin receptor blockers significantly reduce hemoglobin level in patients with type 2 diabetes mellitus not suffered chronic cardiac failure and chronic kidney disease

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Abstract. Anemia due to angiotensin receptor blocker (ARB) therapy has been previously reported in patients with diabetes mellitus with glomerular filtration rates of <60 mL min⁻¹/1.73 m². However, whether Japanese patients with type 2 diabetes mellitus (T2DM) receiving ARB therapy for chronic cardiac failure and chronic kidney disease develop reduced hemoglobin (Hb) levels has not been elucidated. Thus, this cross-sectional study was conducted, and Hb levels were compared between patients with T2DM with and without ARB administration. No significant difference in the prescribed proportion of antidiabetic medicines such as biguanide, sodium glucose co-transporter 2 inhibitors, and α-glucosidase inhibitors was found between the group treated with ARBs and the group without ARBs. Thus, we considered that the effects of antidiabetic medicines on the results were minimum. In this study, the Hb levels of patients who received ARBs (13.8 ± 1.7 g/dL) were significantly lower than those of patients without ARBs (14.9 ± 1.35 g/dL) (p = 0.034). The difference between this study and a previous study relies on eGFR levels. In this study, the eGFR levels of the patients in this study and the previous study were above 60 and below 60 mL min⁻¹/1.73 m², respectively. Despite those differences, both studies showed that the use of ARBs was associated with a decrease in Hb levels in patients with T2DM. Thus, the evaluation of glycated Hb levels should be focused on whether ARBs are prescribed for patients with T2DM.

Key words: Angiotensin receptor blocker, Type 2 diabetes mellitus, Hemoglobin, Glycated hemoglobin

In 2008, Inoue et al. [3] have found that the use of ARBs was associated with a decrease in hemoglobin (Hb) levels in patients with diabetic nephropathy in a retrospective chart review of Japanese patients using ACEIs or ARBs. Of note is the study’s sample, which consisted of patients with a glomerular filtration rate (GFR) <60 mL min⁻¹/1.73 m² [2]. This study was conducted to observe and compare the effects of ARBs on the Hb levels in patients with type 2 DM (T2DM) without diabetic nephropathy.

Materials and Methods

Participants

The study protocol was reviewed and approved by the institutional review board of Saku Central Hospital Advanced Care Center and conducted in accordance to
the Declaration of Helsinki. The patients provided written informed consent before participating in this clinical study.

One hundred and eighty-three patients with T2DM were analyzed at Saku Central Hospital Advanced Care Center. These patients regularly visited the hospital. Patients whose estimated glomerular filtration rate (eGFR) was below 60 mL min \(^{-1}\)/1.73 m\(^2\) were excluded from this study.

We confirmed that no patients showed any signs of cardiac failure on chest X-ray and abnormal values of brain natriuretic peptide. First, we studied which factor affects the Hb levels of the patients using multivariate analysis. As shown in Table 1, age, body length, body weight, eGFR, Biguanide dosage, duration of DM, and ARB administration affect the Hb level independently. Then, the patients were divided into two groups according to the presence \((N = 111)\) or absence \((N = 72)\) of ARBs. Table 2 shows the characteristics of patients with and without ARBs. The mean age of the patients being treated with and without ARBs was 68.58 ± 12.22 years and 64.39 ± 11.28 years, respectively. Moreover, the mean body length of the patients treated with and without ARBs was 158.8 ± 17.9 cm and 161.4 ± 10.02 cm, respectively. The mean body weight was 63.68 ± 16.86 kg and 65.2 ± 12.36 kg for patients with and without ARBs, respectively. For both groups, 60% of the patients were males. The mean eGFR of patients with and without ARBs was 73.95 ± 12.59 mL min \(^{-1}\)/1.73 m\(^2\) and 70.5 ± 14.6 mL/min \(^{-1}\)/1.73 m\(^2\), respectively. The mean urinary albumin/creatinine ratio of subjects with and without ARBs was 39.4 ± 61.8 and 150.8 ± 74.2 per mg/g creatinine, respectively. Consequently, the rate of biguanide (BG) prescription was 27.8% and 29.8% in patients with and without ARBs. The mean prescribed dosage of BG was 670.7 ± 580.3 mg/day and 640.2 ± 529.7 mg/day, respectively, with a mean duration of 4.34 ± 3.57 years and 3.59 ± 3.48 years, respectively, for patients with and without ARBs. In addition, the mean duration of T2DM was 13.43 ± 6.19 and 10.36 ± 8.2 years for patients with and without ARBs, respectively.

The proportion of prescribed antidiabetic medicines was as follows: sodium glucose co-transporter 2 inhibitors (SGLT2is) were prescribed in 10.1% and 10.6% of patients treated with and without ARBs, respectively. BG was prescribed in 27.8% and 29.8% of patients treated with and without ARBs, respectively. Insulin was prescribed in 14.1% and 6.4% of patients treated with and without ARBs, respectively. Sulfonylurea (SU) was prescribed in 8.9% and 6.4% of patients treated with and without ARBs, respectively. Dipeptidyl peptidase-4 inhibitors (DPP4is) were prescribed in 19.0% and 30.9% of patients treated with and without ARBs, respectively. GLP-1 receptor analog was prescribed in 19.0% and 30.9% of patients treated with and without ARBs. Thiazolidinedione (TDZ) was prescribed in 2.4% and 1.1% of patients treated with and without ARBs, respectively. These results are summarized in Table 3.

Table 1 Factors affecting hemoglobin levels analyzed using multivariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>R(^2)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>–0.525</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.159</td>
<td>0.13</td>
</tr>
<tr>
<td>Body length</td>
<td>0.215</td>
<td>0.04</td>
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<tr>
<td>Body weight</td>
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<td>0.004</td>
</tr>
<tr>
<td>HbA1c</td>
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<td>0.408</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.417</td>
<td>0.0001</td>
</tr>
<tr>
<td>BG dosage</td>
<td>0.225</td>
<td>0.031</td>
</tr>
<tr>
<td>Duration with BG administration</td>
<td>0.032</td>
<td>0.765</td>
</tr>
<tr>
<td>Duration with DM</td>
<td>–0.321</td>
<td>0.002</td>
</tr>
<tr>
<td>ARB</td>
<td>–0.316</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Factors affecting hemoglobin levels in the patients in this study were analyzed by multivariate analysis, and the results are summarized in this table. eGFR, estimated glomerular filtration rate; BG, biguanide; DM, diabetes mellitus; R\(^2\), coefficient of determination.

Furthermore, α-glucosidase inhibitors (α-GIs) were prescribed in 7.3% and 7.4% of patients treated with and without ARBs, respectively. GLP-1 receptor analog was prescribed in 6.0% and 1.0% of patients treated with and without ARBs, respectively. Glinide was prescribed in 4.4% and 6.4% of patients treated with and without ARBs, respectively. Thiazolidinedione (TDZ) was prescribed in 2.4% and 1.1% of patients treated with and without ARBs, respectively. These results are summarized in Table 3 with \(p\) values based on the chi-square test. The proportions of the prescribed ARBs were the following: Candesartan, Azilsartan, Olmesartan, Valsartan, Irbesartan, Telmisartan, and Losartan were prescribed in 31.1%, 21.8%, 20.7%, 11.5%, 9.2%, 3.4%, and 2.3% of the patients, respectively. These results are summarized in Table 4.

### Study design

**Study 1.** BG caused anemia by disrupting vitamin B12 absorption in foreign countries [4] but did not seem to cause anemia in Japan [5]. This discrepancy was investigated by confirming whether BG causes anemia in the patients assessed in this study. HB levels were compared between patients who were not prescribed with both ARBs and BG and those who were prescribed with BG but not ARBs.

**Study 2.** Next, the Hb levels were compared between patients treated with and without ARBs to determine whether ARBs reduce Hb levels in Japanese patients with T2DM whose eGFR was above 60 mL min \(^{-1}\)/1.73 m\(^2\).
**Statistical analysis**

A computerized program, SPSS 10.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analysis. All numerical values were expressed as means ± SD. Multiple comparisons of the variable were performed using Dunnett’s test. Group comparisons of continuous variables were performed using analysis of variance and Wilcoxon rank-sum test for non-normally distributed data. The chi-square test was used for categorical variables. All tests for significance and the resulting \( p \) values were two-sided with a level of significance set at 5%.

**Results**

**Study 1. BG did not cause anemia**

The Hb levels of the patients who were not prescribed with both ARBs and BG were 14.3 ± 1.3 g/dL. However, the Hb levels of those who were prescribed with BG but not ARBs were 14.88 ± 1.6 g/dL. Thus, the Hb levels of both groups did not show a statistical difference. Therefore, BG did not cause anemia in the patients of this study, which conforms to the results of other studies in Japan [5].

**Study 2. The administration of ARBs reduces the Hb levels**

Patients who were prescribed with BG were included in study 2 because BG did not induce anemia in the patients of this study as described above. In addition, the proportion of prescribed BG was similar between patients who were treated with and without ARBs (27.8% vs. 29.8%, respectively) (Table 2).

As shown in Table 5, the Hb levels of the patients treated with and without ARBs were 13.8 ± 1.7 and 14.9 ± 1.35 g/dL, respectively. Thus, a statistical significance was found between both groups (\( p = 0.034 \)). In addition, this study confirmed that Hb levels before ARB treatment was 14.5 ± 1.46 g/dL and was significantly higher compared with that of after ARB treatment (13.8 ± 1.7 g/dL).
vs. 14.5 ± 1.46 g/dL; \( p = 0.0019 \)). The mean corpuscular volume was 90.8 ± 7.5 fL and 91.3 ± 4.0 fL in patients with and without ARBs, respectively. In addition, the mean corpuscular Hb (MCH) and mean corpuscular Hb concentration (MCHC) were 30.4 ± 2.1 pg and 30.5 ± 1.4 pg, respectively, and 33.5% ± 3.7% and 33.4% ± 0.9%, respectively, in patients with and without ARBs. Those values were not statistically significant between both groups.

**Discussion**

In this study, the use of ARBs was associated with a decrease in Hb levels. However, the mechanism of action of ARBs and their effects on Hb levels remain unclear. One possible mechanism is that angiotensin 2 increases the proliferation of early erythroid progenitors but not the progenitors of other cell lines, and ARBs completely abolish this effect [6]. Those observations suggested a possible inhibitory effect of ARBs on the bone marrow.

Table 3 shows that the prescribed proportion of antidiabetic medicines such as DPP4i, BG, SGLT2is, SU, and \( \alpha \)-GIs was not different between groups treated with and without ARBs. Thus, the effect of antidiabetic medicines on the results was negligible in this clinical study.

This study presented results that determined the effect of ARB medications on Hb levels. The eGFR level is one of the differences between the current and previous studies. The eGFR level in the current and previous studies was >60 [7] and <60 mL min\(^{-1}/1.73 \) m\(^2\), respectively. Despite of those differences, both studies showed that the usage of ARBs was associated with a decrease in Hb in patients with T2DM. Thus, the use of ARBs was associated with lower Hb in patients with T2DM but without chronic kidney disease.

**Conclusion**

Attention should be focused on Hb levels when ARBs are prescribed for patients with T2DM.

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**Disclosure**

**Conflicts of interest disclosures**

No authors have any potential conflicts of interest associated with this clinical work.

**Competing interests**

The authors declare no significant competing financial, professional, or personal interests that may have influenced the performance or presentation of the work described in this manuscript.
References