

Effects of Rebamipide on Gastrointestinal Symptoms in Patients with Type 2 Diabetes Mellitus (*Diabetes Metab J* 2016;40:240-7)

Sejeong Park¹, So Young Park¹, Sang Youl Rhee^{1,2}

¹Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul,

²Research Institute of Endocrinology, Kyung Hee University, Seoul, Korea


We appreciate the interests and comments on our manuscript, “Effects of rebamipide on gastrointestinal symptoms in patients with type 2 diabetes mellitus,” which was published in *Diabetes & Metabolism Journal* (DMJ) [1].

Atypical gastrointestinal (GI) symptoms present more commonly in diabetic patients than in the general population [2]. Although various drugs have been applied to improve GI symptoms, medical treatment of diabetic gastropathy remains challenging due to the numerous side effects and limitations of pre-existing drugs. Rebamipide is a gastro-protective drug with prostaglandin- and mucus glycoprotein synthesis-stimulating properties [3]. Its clinical effects of healing ulcer and preventing ulcer recurrence have been proved through previous studies. However, there is currently little evidence regarding its effects on GI symptoms in type 2 diabetes mellitus (T2DM).

Our study was performed to evaluate the effects of rebamipide on atypical GI symptoms in T2DM patients. A total of 107 patients were enrolled, and 84 patients completed the study [1]. By comparing the diabetes bowel symptom questionnaire (DBSQ) scores before and after the rebamipide treatment, we concluded that it is effective in improving atypical GI symptoms of T2DM patients. Besides simply confirming the effect of the drug, our results suggest the need of a systematic approach to improve quality of life of T2DM patients. We believe that it is worth being published in a prominent journal such as DMJ.

As mentioned in the letter, our study did not fully consider the confounding impact of incretin-based therapy on GI symptoms. This is because the protocol of the study was established before the wide use of incretin-based therapy. Among participants, 17 were taking dipeptidyl peptidase-4 (DPP-4) inhibitor and none were prescribed with glucose-like peptide-1 agonist. Subgroup analysis according to the use of DPP-4 inhibitors showed statistically significant change of DBSQ score after rebamipide treatment in some of the questionnaire (Fig. 1). However, when the differences of the DBSQ scores before and after the rebamipide were compared between two groups, no significant differences were observed (Table 1).

We also agree with the opinion that not many objective tests were done in our study. Not all of the subjects underwent endoscopic and/or other imaging analyses that could rule out other organic GI disease or demonstrate the change of functional status in a more objective way. This is because it was an investigator-initiated clinical trial conducted with a limited budget. Although it could be an important limitation of our study, we statistically analyzed the changes of GI symptoms through a well-organized questionnaire instead of performing various diagnostic tests. The DBSQ applied in our study consisted of 10 detailed questions regarding upper and lower GI symptoms. Each question of the DBSQ were systematically organized based on the elements of other questionnaires that have previously been validated [4,5]. In subgroup analyses,

Corresponding author: Sang Youl Rhee  <http://orcid.org/0000-0003-0119-5818>
Department of Endocrinology and Metabolism, Kyung Hee University
School of Medicine, 23 Kyungheedaero, Dongdaemun-gu, Seoul 02447,
Korea
E-mail: bard95@hanmail.net

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

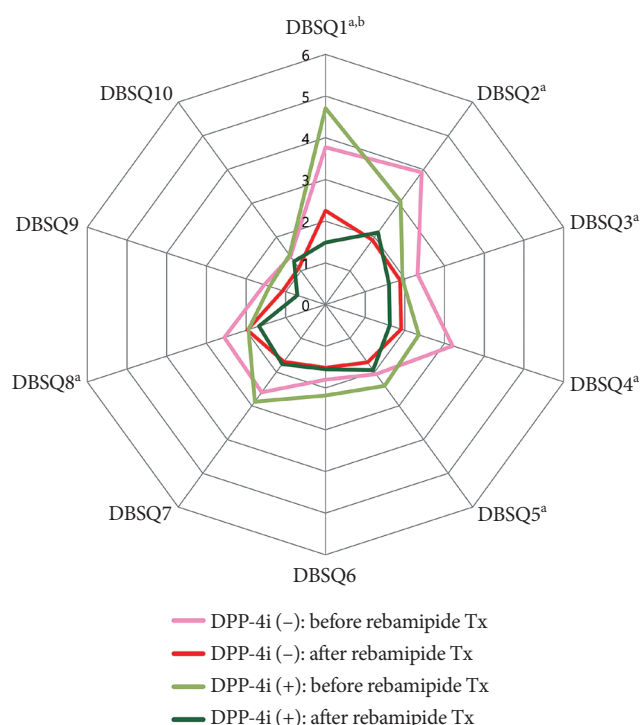


Fig. 1. Comparison of the diabetes bowel symptom questionnaire (DBSQ) scores between before and after rebamipide treatment according to dipeptidyl peptidase-4 inhibitor (DPP-4i) administration. Wilcoxon's signed rank test. Tx, treatment. ^a $P < 0.05$, DPP-4i (-) group, ^b $P < 0.05$, DPP-4i (+) group.

improvement of GI symptoms were observed consistently throughout all subgroups analyses for age, duration of diabetes, glycated hemoglobin level, and body mass index. One exception was observed with the subgroup analysis for sex, which only showed a significant improvement in female subgroup only. As we have mentioned in the original article, we think this is because of the higher number of female subjects ($n = 79$, 75.2%) compared with males ($n = 26$, 24.8%) [1].

On the basis of the implications of this study, we are attempting a larger-scale multicenter clinical study regarding symptomatic improvement of T2DM patients. We would like to thank Dr. Kim for the interest and thoughtful comments. We believe that it would be a good guide in conducting future studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

Table 1. Comparison of the DBSQ score change after rebamipide treatment between two subgroups divided by the use of DPP-4i

Variable	DPP-4i (+)	DPP-4i (-)	P value ^a
Pre-post DBSQ1	1.06 ± 2.08	1.18 ± 1.63	0.449
Pre-post DBSQ2	0.94 ± 1.84	0.59 ± 1.87	0.444
Pre-post DBSQ3	0.66 ± 1.82	0.41 ± 1.58	0.647
Pre-post DBSQ4	0.72 ± 1.92	0.18 ± 1.33	0.275
Pre-post DBSQ5	0.48 ± 1.40	0.88 ± 2.34	0.645
Pre-post DBSQ6	-0.08 ± 1.38	-0.12 ± 1.27	0.765
Pre-post DBSQ7	0.11 ± 1.39	0.53 ± 1.51	0.309
Pre-post DBSQ8	0.62 ± 1.77	-0.06 ± 1.82	0.129
Pre-post DBSQ9	0.20 ± 0.85	0.24 ± 0.56	0.698
Pre-post DBSQ10	0.12 ± 0.93	0.06 ± 0.66	0.666
Pre-post DBSQ total	4.65 ± 6.14	3.88 ± 5.18	0.583

Values are presented as mean ± standard deviation. Pre-post calculated by subtracting the scores after rebamipide treatment from the initial scores.

DBSQ, diabetes bowel symptom questionnaire; DPP-4i, dipeptidyl peptidase-4 inhibitor.

^aP value determined using Wilcoxon's signed rank test.

REFERENCES

1. Park S, Park SY, Kim YJ, Hong SM, Chon S, Oh S, Woo JT, Kim SW, Kim YS, Rhee SY. Effects of rebamipide on gastrointestinal symptoms in patients with type 2 diabetes mellitus. *Diabetes Metab J* 2016;40:240-7.
2. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 2001;161:1989-96.
3. Arakawa T, Higuchi K, Fujiwara Y, Watanabe T, Tominaga K, Sasaki E, Oshitani N, Yoshikawa T, Tarnawski AS. 15th Anniversary of rebamipide: looking ahead to the new mechanisms and new applications. *Dig Dis Sci* 2005;50 Suppl 1:S3-11.
4. Talley NJ, Phillips SF, Melton J 3rd, Wiltgen C, Zinsmeister AR. A patient questionnaire to identify bowel disease. *Ann Intern Med* 1989;111:671-4.
5. Quan C, Talley NJ, Cross S, Jones M, Hammer J, Giles N, Horowitz M. Development and validation of the Diabetes Bowel Symptom Questionnaire. *Aliment Pharmacol Ther* 2003;17:1179-87.