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Association between the *Blautia/Bacteroides* Ratio and Altered Body Mass Index after Bariatric Surgery

Yoonhong Kim[1,*], Dooheon Son[2,*], Bu Kyung Kim[3], Ki Hyun Kim[1], Kyung Won Seo[1], Kyoungwon Jung[3], Seun Ja Park[3], Sanghyun Lim[2], Jae Hyun Kim[3]

[1]Department of Surgery, Kosin University College of Medicine, Busan; [2]Cell Biotech Co. Ltd., Gimpo; [3]Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Background: Current evidence support that the gut microbiota plays a potential role in obesity. Bariatric surgery can reduce excess weight and decrease the risk of life-threatening weight-related health problems and may also influence gut microbiota. In this study, we aimed to investigate the changes in gut microbiota before and after bariatric surgery and evaluate the association of the gut microbial shift and altered body mass index (BMI) after bariatric surgery.

Methods: Between January 2019 and July 2020, stools from 58 patients scheduled for bariatric surgery were collected. Six months after bariatric surgery, stools from 22 of these patients were re-collected, and the changes in gut microbiota before and after bariatric surgery were evaluated. In addition, the differences in gut microbiota between patients with severe obesity (BMI >35 kg/m^2, n=42) and healthy volunteers with normal BMI (18.8 to 22.8 kg/m^2, n=41) were investigated.

Results: The gut microbiota of patients who underwent bariatric surgery showed increased α-diversity and differed β-diversity compared with those before surgery. Interestingly, *Blautia* was decreased and *Bacteriodes* was increased at the genus level after bariatric surgery. Further, the *Blautia*/*Bacteroides* ratio showed a positive correlation with BMI. To validate these results, we compared the gut microbiota from severely obese patients with high BMI with those from healthy volunteers and demonstrated that the *Blautia*/*Bacteroides* ratio correlated positively with BMI.

Conclusion: In the gut microbial analysis of patients who underwent bariatric surgery, we presented that the *Blautia*/*Bacteroides* ratio had changed after bariatric surgery and showed a positive correlation with BMI.

Keywords: Obesity; Bariatric surgery; Gastrointestinal microbiome

INTRODUCTION

Obesity is defined as excessive fat accumulation with body mass index (BMI) over 30 (defined as a BMI over 25 kg/m^2 according to the Asia-Pacific perspective) and presents a risk to health. Globally, a total of 609 million adults were estimated to

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Corresponding authors: Jae Hyun Kim
Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-5061, **Fax:** +82-51-990-5055, **E-mail:** kjh8517@daum.net

Sanghyun Lim
Cell Biotech Co. Ltd., 50 Aegibong-ro 409beon-gil, Wolgot-myeon, Gimpo 10003, Korea
Tel: +82-31-987-6205, **Fax:** +82-31-987-6209, **E-mail:** shlim@cellbiotech.com

*These authors contributed equally to this work.

be obese in 2015 [1]. Obesity is associated with cardiovascular disease, diabetes mellitus (DM), several types of cancers, musculoskeletal disorders, and poor mental health [2-5]. The etiologies of obesity are genetic, behavioral, environmental, physiological, social, and cultural, resulting in energy imbalance and promoting excessive fat deposition [6]. Recently, emerging evidence has suggested that gut microbiota plays a role in obesity. Since the first reporting in 2006 about the metabolic potential of mouse gut microbiota with increased capacity for energy harvest [7], there have been numerous studies reporting an association between obesity and gut microbiota. In particular, obese individuals tend to have an elevated Firmicutes-to-Bacteroidetes ratio compared with lean individuals, and this ratio is similar to that found in children [8-11].

Bariatric surgery is the most effective treatment option for obesity, which archives rapid and durable weight loss and has dramatic effects on remission of type 2 DM. It also can lead to improvements in the atherosclerotic process, hypertension, obstructive sleep apnea, and cardiovascular related mortality [12,13]. Bariatric procedures include laparoscopic sleeve gastrectomy (LSG), which primarily restricts limiting food intake, and laparoscopic Roux-en-Y gastric bypass (LRYGB), which induces restriction/malabsorption. Both procedures have remarkable metabolic effects, such as increased glucose tolerance, insulin sensitivity, and secretions of incretin and glucagon like peptide-1 [14]. Recent studies have reported that bariatric surgery induces significant shifts in gut microbiota and may contribute to weight loss and metabolic changes [15-17]. The anatomic rearrangements of bariatric surgery mainly affect the proximal intestine, and bariatric surgery could impact the composition and activity of the resident gut microbiota [18]. Although there is increasing evidence for the effectiveness of bariatric surgery on gut microbiota, the understanding for the contribution of gut microbiota to the induction and maintenance of weight loss and the resolution of related comorbidities is not fully understood. Most evidence for the relationship between gut microbiota and bariatric surgery has been limited to the Western population; data on the Eastern population has rarely been reported.

In this study, obese Korean patients who underwent bariatric surgery in a single institution were enrolled. Differences in gut microbiota before and after bariatric surgery were evaluated. We hypothesized that the composition and distribution of the gut microbiota changed after bariatric surgery and that these transitions are associated with alteration of BMI. The aim of this study was to investigate the change of gut microbiota before and after bariatric surgery and evaluate the association of gut microbial shift and altered BMI after bariatric surgery.

METHODS

Patients and stool collection

Patients who were between 18 and 60 years of age and who scheduled bariatric surgery, either a LSG or LRYGB, were included, and patients who had any cancer or severe lung, liver, kidney, or heart disease were excluded. A study investigator explained the aim and contents of the study in detail to the patients, and all patients provided written informed consent. Detailed clinical data including age, sex, height, weight, a presence of sleep apnea or gastroesophageal reflux disease, and history of medication uses for DM, hypertension, dyslipidemia, depression, or musculoskeletal pain were collected through a self-administered questionnaire or medical records. Between January 2019 and July 2020, fecal samples were collected from 58 patients who scheduled bariatric surgery. Six months after bariatric surgery, fecal samples of 22 patients were re-collected, and the change of gut microbiota before and after bariatric surgery was evaluated. In addition, we selected fecal samples of 42 patients with severe obesity (BMI >35 kg/m^2) from the 58 patients who scheduled bariatric surgery and compared to those of healthy volunteers with normal BMI (n=41) for validation. The collected samples were stored at –80°C in a deep freezer and transported to Cell Biotech Co. Ltd. (Gimpo, Korea) for analysis. In addition, the differences in gut microbiota between patients who have preoperative severe obesity (BMI >35 kg/m^2, n=42) and healthy volunteers with normal BMI (18.8 to 22.8 kg/m^2, n=41) were investigated. The study protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital (KUGH 2021-08-012).

DNA extraction and sequencing

Microbial DNA was extracted using the FastDNA SPIN Kit for Soil (MP Biochemicals, Santa Ana, CA, USA) according to the manufacturer's instructions. The extracted microbial DNA was purified using DNeasy PowerClean Cleanup Kit (Qiagen, Hilden, Germany), and DNA quality was measured using Nanodrop. The purified DNA was measured for DNA concentration using the Qubit dsDNA BR Assay kit (Thermo Fisher Scientific, Carlsbad, CA, USA).

A sequencing library was prepared according to the Illumina 16S Metagenomic Sequencing Library Preparation Guide. The V4-V5 region of the bacterial 16S rRNA gene was amplified for

16S rRNA gene sequencing. The forward primer in the v4 region (CCA GCM GCC GCG GTA ATW C) and the reverse primer in the V5 region (CC GTC AAT TYY TTT RAG TTT) were used for polymerase chain reaction amplification in this study. The amplified sequencing library was purified with Agencourt AMPure XP beads (Beckman Coulter, Brea, CA, USA) and the quality of the library was checked using a 2100 Bio-analyzer (Agilent, Santa Clara, CA, USA). The library pool was sequenced with 250 bp paired-end reads on the MiSeq platform (Illumina, San Diego, CA, USA) using the MiSeq reagent kit V2 (Illumina).

Statistical analysis

Raw sequencing data were processed using the Quantitative Insight into Microbial Ecology software package 2 (QIIME 2, v 2019.10, http://qiime2.org). Denoising was performed using DADA2, and a taxonomy table was created using the Greengenes database (v13_8) normalized to a depth of 63,000, which was the minimum depth of the sample was used for alpha and beta diversity analysis. Data visualization was performed using the ggplot package of R (v4.0.3, R Foundation for Statistical Computing, Vienna, Austria) and statistical analyses were performed through Wilcoxon signed rank test and permutational multivariate analysis of variance (PERMANOVA) using the vegan package.

RESULTS

Baseline characteristics and alteration of body profile after bariatric surgery

The baseline characteristics of 22 patients who provided their fecal samples before and after bariatric surgery are summarized in Table 1. The mean age was 37.8 years and eight of the 22 patients (36.4%) were male. More than half of the patients had comorbidities, including DM, hypertension, and sleep apnea. Before bariatric surgery, the mean body weight of patients was 106.8 kg (range, 67.3 to 166.0), and the mean BMI was 39.2 kg/m^2 (range, 30.1 to 62.1). Six months after bariatric surgery, the body weight and BMI of patients decreased to an average 84.2 kg (range, 55.1 to 142.8) and 30.6 kg/m^2 (range, 22.3 to 45.6), respectively (Fig. 1A).

Table 1. Baseline Characteristics of Enrolled Patients

Characteristic	Total (n=22)
Age, yr	37.8 (21–64)
Sex	
Male	8 (36.4)
Female	14 (63.6)
Comorbidities	
Diabetes mellitus	14 (63.6)
Hypertension	12 (54.5)
Depression	1 (4.5)
Musculoskeletal pain	4 (18.2)
Sleep apnea	14 (63.6)
Dyslipidemia	7 (31.8)
GERD	2 (9.1)
Body weight, kg	106.8 (67.3–166.0)
BMI, kg/m^2	39.2 (30.1–62.1)
Type of surgery	
LSG	14 (63.6)
LRYGB	8 (36.4)

Values are expressed as mean (range) or number (%).
GERD, gastroesophageal reflux disease; BMI, body mass index; LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass.

Changes in gut microbial diversity and composition before and after bariatric surgery

Compared with before bariatric surgery, alpha diversity significantly increased and beta diversity differed after surgery (Fig. 1B). After bariatric surgery, Firmicutes decreased and Bacteroidetes increased at the phylum level, and the taxonomy composition at the genus level was remarkably changed (Fig. 1C). We performed linear discriminant analysis (LDA) effect size to compare the gut microbial changes at the genus level following bariatric surgery. The LDA scores were computed for features that showed differential abundance of patients before and after bariatric surgery. As shown in Fig. 2A, at the genus level *Blautia*, *Catenibacterium*, and *Clostridiaceae* were enriched in patients before bariatric surgery, whereas *Bacteroides* and *Streptococcus* were the preponderance in patients after bariatric surgery. In addition, we performed LDA effect size analysis at the species level and identified that *Ruminococcus gnavus* and *Blautia obeum wexlerae* were enriched in patients before bariatric surgery, whereas *Bacteroides thetaiotaomicron*, *Bacteroides nordii*, *Bacteroides uniformis*, and *Bacteroides dorei vulgatus* were the preponderance in patients after bariatric surgery (Supplemental Fig. S1A).

Correlation between a specific gut microbiome and BMI

Based on the results of LDA scores, we evaluated the correla-

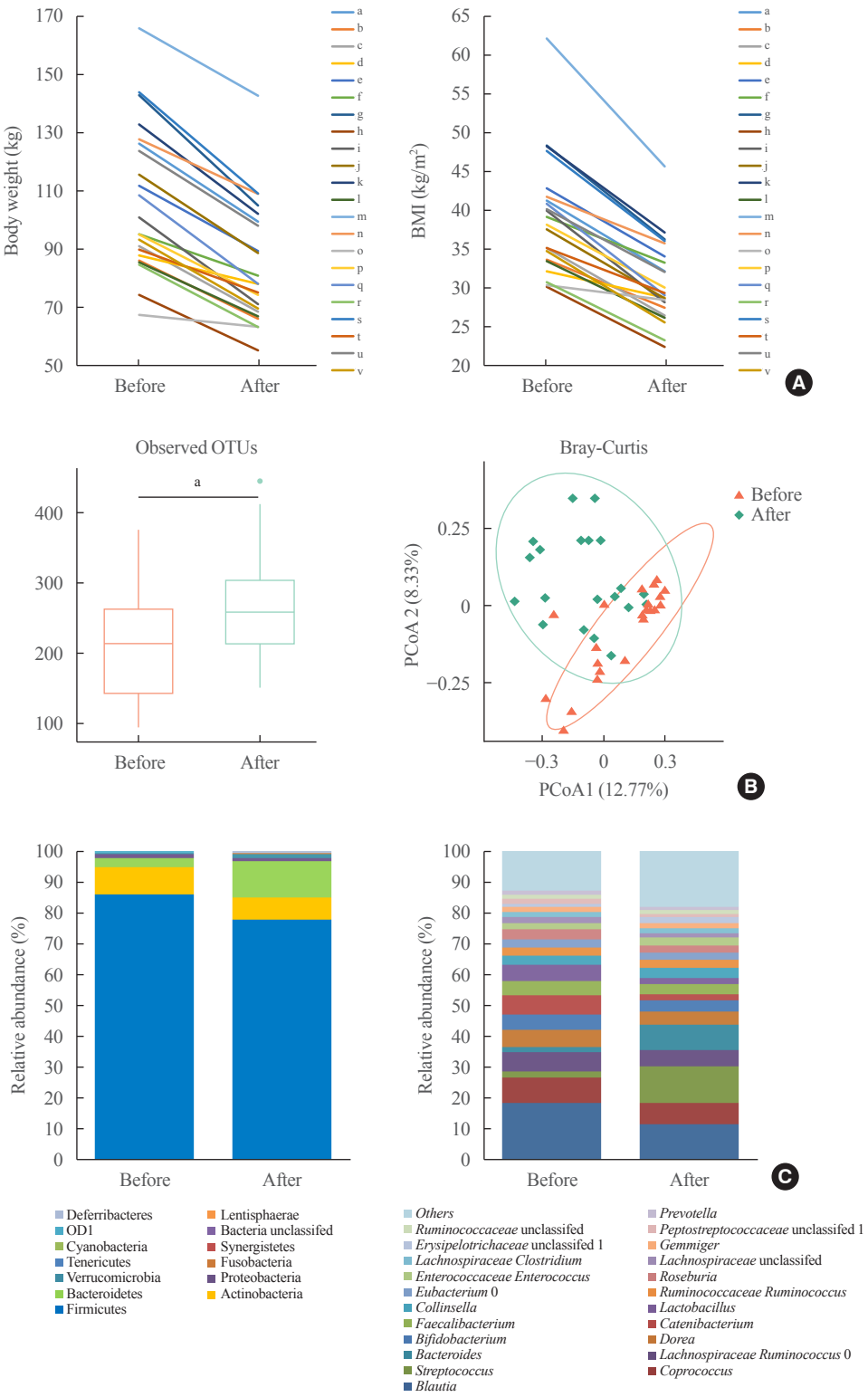

Fig. 1. Changes of body profiles and gut microbiota after bariatric surgery. (A) Individual changes of body weight and (left panel) body mass index (BMI; right panel) after bariatric surgery. (B) Comparison of alpha diversity (left panel) and beta diversity (right panel) before and after bariatric surgery. (C) Alteration of taxonomy composition after bariatric surgery at the phylum level (left panel) and genus level (right panel). OTU, operational taxonomic unit; PCoA, principal coordinates analysis. [a]$P<0.05$.

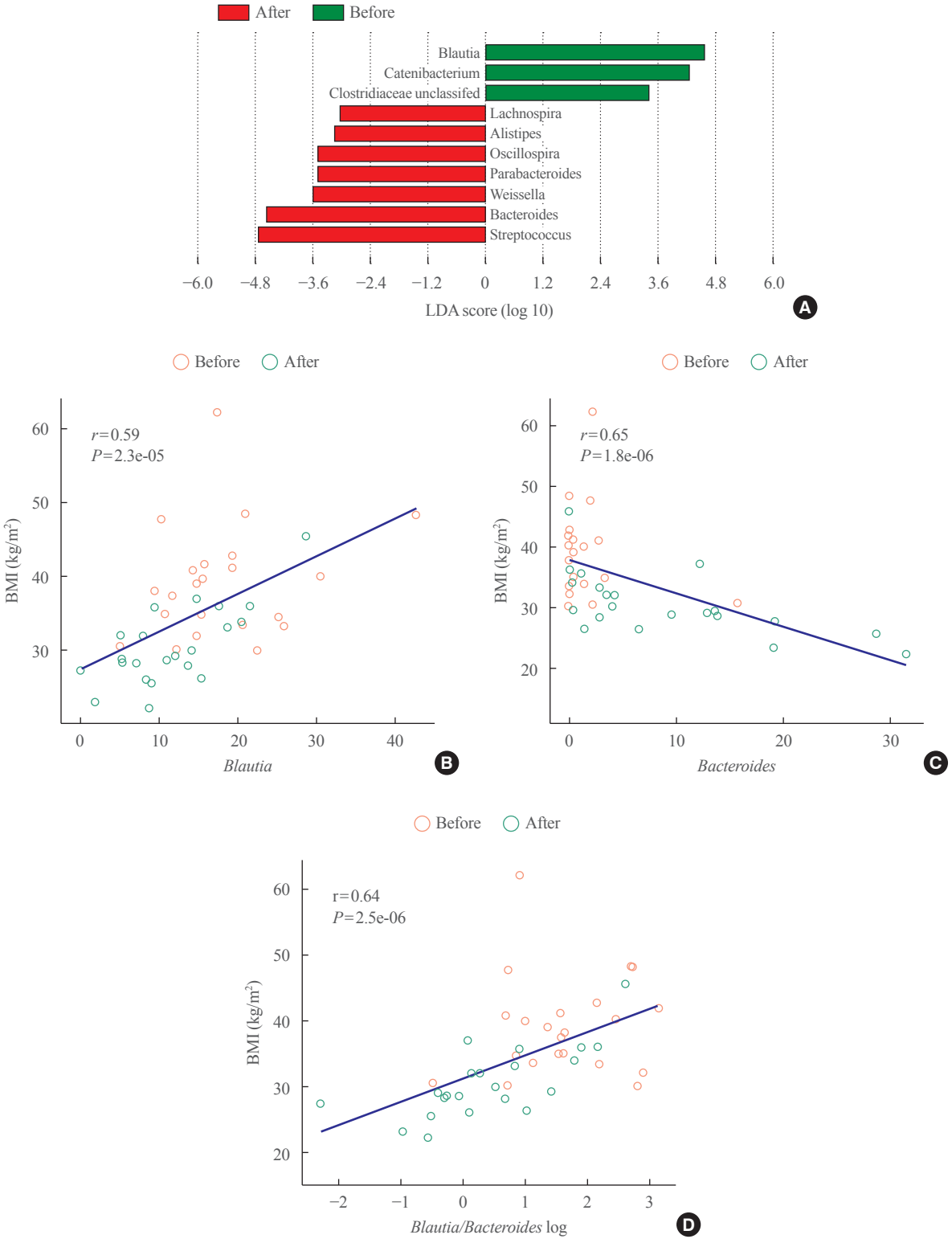

Fig. 2. Prominent gut microbiota at the genus level before and after bariatric surgery and correlation with body mass index (BMI). (A) Linear discriminant analysis (LDA) effect size before and after bariatric surgery (threshold 2.4). (B) Correlation between *Blautia* and BMI. (C) Correlation between *Bacteroides* and BMI. (D) Correlation between the log value of *Blautia*/*Bacteroides* and BMI.

tion analysis between gut microbiota at the genus level and BMI and found that *Blautia* showed a positive correlation with BMI (r=0.59, P=2.3×10^{-5}) while *Bacteroides* had a negative correlation with BMI (r=–0.65, P=1.8×10^{-6}) (Fig. 2B, C, Supplemental Table S1). The abundance of *Blautia* significantly decreased and the abundance of *Bacteroides* significantly increased after bariatric surgery (Supplemental Fig. S2). When converting as a log value, we identified that the log value of the *Blautia*/*Bacteroides* ratio showed a positive correlation with BMI (Fig. 2D). In addition, we found a correlation between gut microbiota at the species level and BMI; *Ruminococcus gnavus* and *Blautia obeum wexlerae* showed positive correlations with BMI, while *Bacteroides thetaiotaomicron*, *Bacteroides nordii*, *Bacteroides uniformis*, and *Bacteroides dorei vulgatus* had negative correlations with BMI (Supplemental Fig. S1B, C).

Comparison according to the surgery type

Before surgery, the median body weight and BMI were higher in patients who underwent LSG than those in patients who underwent LRYGB, and these values significantly decreased after both LSG and LRYGB surgery (Supplemental Fig. S3A). Alpha diversity significantly increased in patients who underwent LRYGB, but not in patients who underwent LSG. Further, beta diversity of before and after surgery was significantly differ in

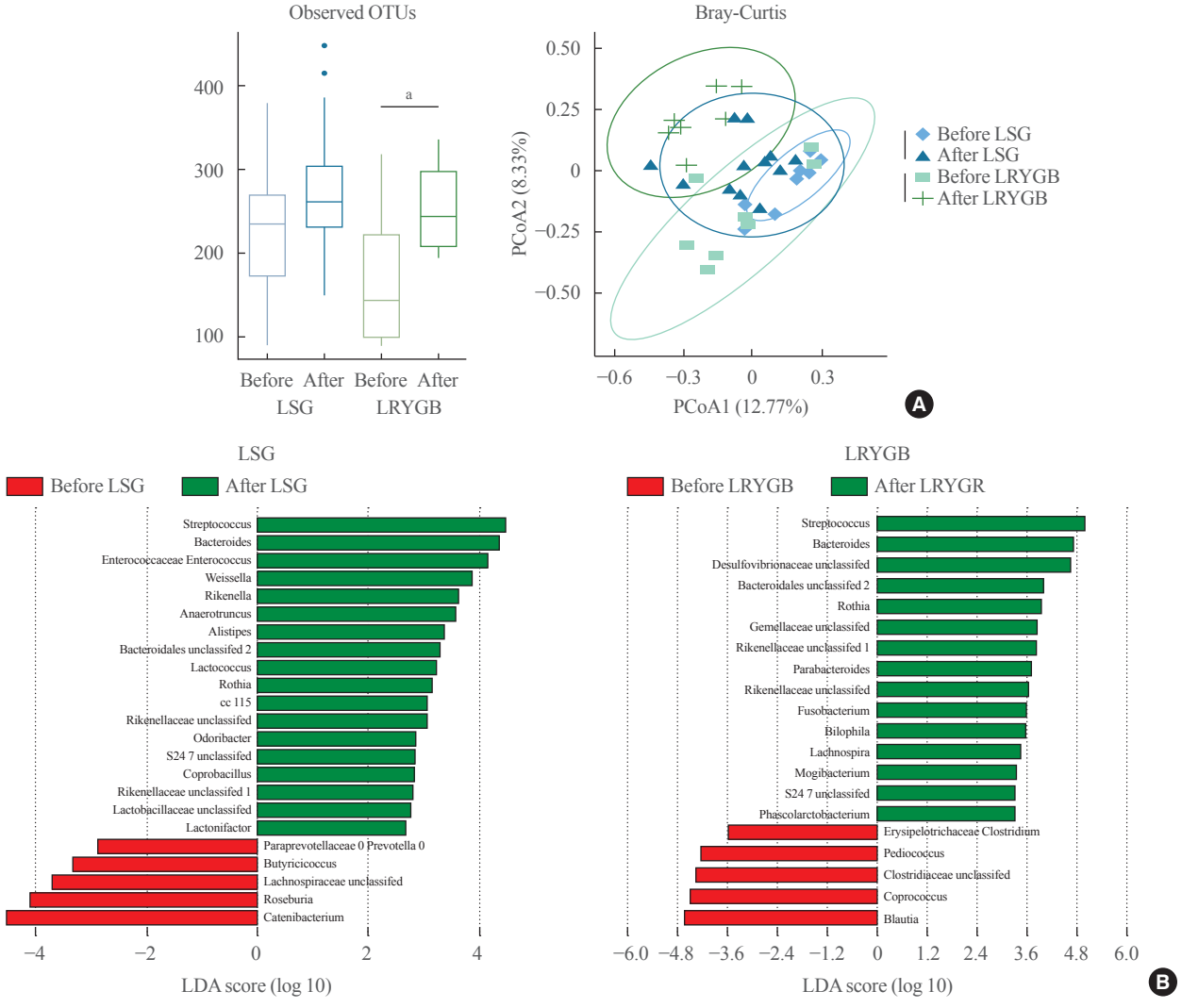

Fig. 3. Comparison of altered gut microbiota after bariatric surgery according to the surgery type. (A) Comparison of alpha diversity (left panel) and beta diversity (right panel) according to surgery type before and after bariatric surgery. (B) Linear discriminant analysis (LDA) effect size before and after laparoscopic sleeve gastrectomy (LSG; left panel). LDA effect size before and after laparoscopic Roux-en-Y gastric bypass (LRYGB; right panel). (C) Correlation between the log value of *Blautia*/*Bacteroides* and body mass index (BMI) in both two surgery types. OTU, operational taxonomic unit; PCoA, principal coordinates analysis. [a]P<0.5. (*Continued to the next page*)

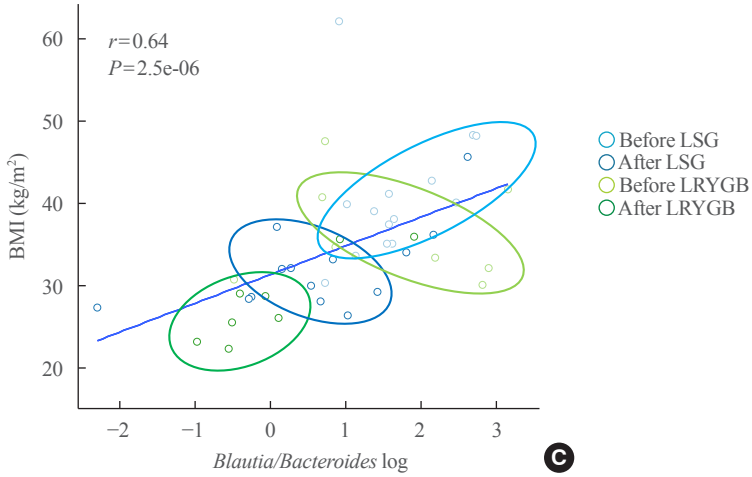

Fig. 3. Continued

both surgery types (Fig. 3A). The taxonomy composition at the phylum and genus levels showed changes after both LSG and LRYGB (Supplemental Fig. S3B). LDA effect size at the genus level showed similar results regardless of the surgery type (Fig. 3B). Further, the log value of the *Blautia*/*Bacteroides* ratio showed a positive correlation with BMI in both surgery types (Fig. 3C).

Validation in severely obese patients and healthy volunteers

To validate these results, we selected 42 patients with severe obesity (BMI >35 kg/m^2) from the 58 patients who were initially enrolled in this study for scheduled bariatric surgery and compared them to the healthy volunteers with normal BMI (n=41). The baseline characteristics of patients with high BMI and healthy controls are summarized in Table 2. Compared to a healthy person, severely obese patients showed different beta diversity, but alpha diversity was not significantly differed (Fig. 4A). The taxonomy composition of severely obese patients was different than those of healthy volunteers; severely obese patients showed more enriched Firmicutes and deficient Bacteroidetes at the phylum level and more abundant *Blautia* and deficient *Bacteroides* at the genus level (Fig. 4B).

The results of LDA effect size demonstrated that *Blautia*, *Streptococcus*, *Ruminococcus_0*, *Catenibacterium*, *Collinsella*, *Eubacterium_0*, *Dorea*, *Lactobacillus* and *Clostridium* were much more enriched in severely obese patients, whereas *Bacteroides*, *Faecalibacterium*, *Ruminococcus*, *Enterococcus*, *Rhizobium*, *Oscillospira*, *Alistipes*, *Lactococcus*, *Paraprevotella*, and *Parabacteroides* were enriched in healthy volunteers. These results were similar in the cladogram analysis (Fig. 5A). In addition, we evaluated the correlation analysis between BMI and gut microbiota of severely obese patients and healthy volunteers, and we found that *Blautia* showed a positive correlation with BMI and *Bacteroides* had a negative correlation with BMI (Fig. 5B, C). We also identified that the log value of the *Blautia*/*Bacteroides* ratio showed a positive correlation with BMI (Fig. 5D).

Table 2. Baseline Characteristics between Healthy Volunteer with Normal Body Weight (BMI, 18.8–22.8 kg/m^2) and Patients with Severe Obesity (BMI >35 kg/m^2)

Characteristic	Healthy volunteers (n=41)	Patients with severe obesity (n=42)
Age, yr	35.9 (22–59)	36.8 (19–58)
Sex		
Male	13 (31.7)	19 (45.2)
Female	28 (68.3)	23 (54.8)
BMI, kg/m^2	20.9 (18.8–22.8)	42.5 (35.1–62.1)
Comorbidities		
Diabetes mellitus	0	19 (45.2)
Hypertension	0	17 (40.5)
Depression	0	5 (11.9)
Musculoskeletal pain	0	6 (14.3)
Sleep apnea	0	36 (85.7)
Dyslipidemia	0	13 (31.0)
GERD	0	7 (16.7)

Values are expressed as mean (range) or number (%).
BMI, body mass index.

DISCUSSION

Despite the increasing evidence of relevance between gut mi-

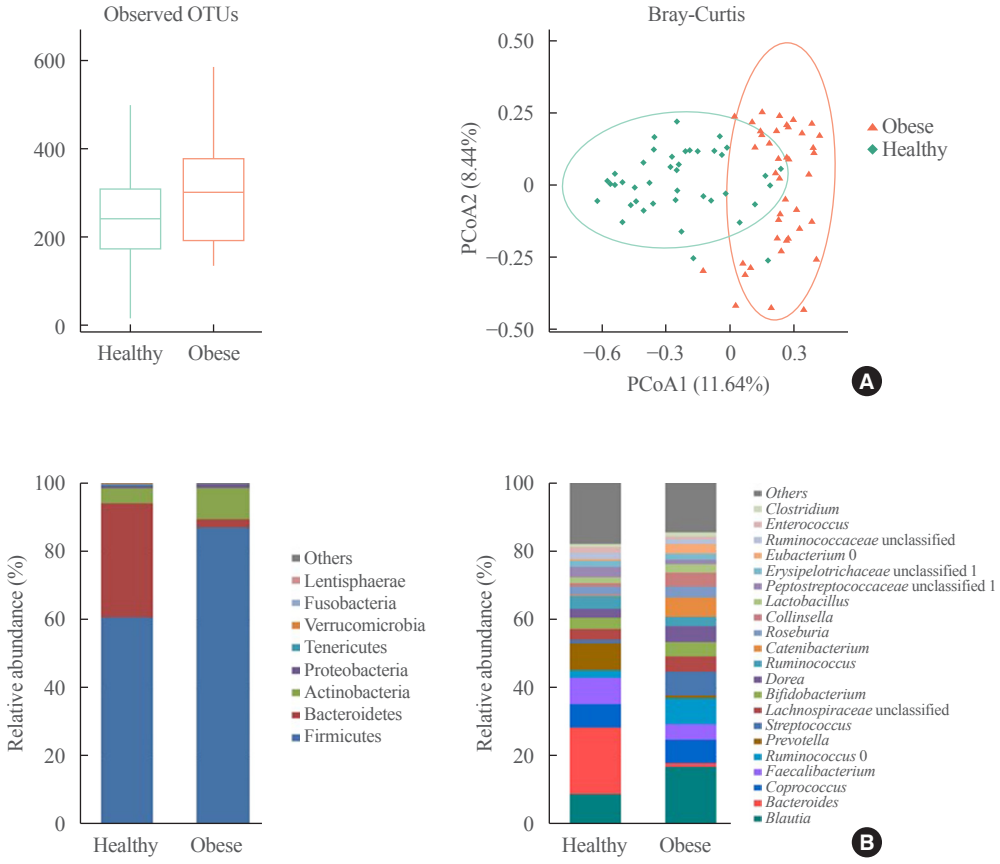

Fig. 4. Comparison of gut microbiota between severely obese patients and healthy controls. (A) Comparison of alpha diversity (left panel) and beta diversity (right panel) between severely obese patients and healthy controls. (B) Comparison of taxonomy composition at the phylum level (left panel) and genus level (right panel) between severely obese patients and healthy controls. OTU, operational taxonomic unit; PCoA, principal coordinates analysis.

crobiota and obesity, the clinical significance for differences in gut microbiota before and after bariatric surgery is under-investigated. This study provides evidence for the association of gut microbial shift and altered BMI after bariatric surgery.

The gut microbiota has evolved along with humans to form symbiotic relationships that are important for life. Emerging data supports a link between the gut microbiota and obesity, suggesting that specific microbiomes could increase the capacity to harvest energy from the diet, leading to obesity [7]. One study found that cohousing lean and obese mice prevented the development of increased adiposity and body mass and showed that the microbiota's metabolic profile of obese mice transformed to a lean-like state [19]. We collected the fecal samples from 58 obese patients who scheduled bariatric surgery and re-collected samples from 22 patients 6 months after bariatric surgery. We then evaluated changes in the gut microbiome before and after bariatric surgery. We observed increased alpha diversity and differed beta diversity after bariatric surgery as well as changes in specific microbiomes after bariatric surgery. Compared to previous studies that have described higher Firmicutes/Bacteroidetes ratios in obese patients versus their healthy counterparts at the phylum level [20-22]. our study shows that the *Blautia*/*Bacteroides* ratio is associated positively with BMI at the genus level. In addition, we presented that *Ruminococcus gnavus* and *Blautia obeum wexlerae* were enriched in patients before bariatric surgery, whereas *Bacteroides thetaiotaomicron*, *Bacteroides nordii*, *Bacteroides uniformis*, and *Bacteroides dorei vulgatus* were enriched in patients after bariatric surgery. These results suggest that gut microbial changes occur after bariatric surgery and that specific microbiomes might be strongly associated with obesity.

A study using next-generation sequencing reported that certain bacterial species including *Blautia huydrogenotorophica*, *Coprococcus catus*, *Eubacterium ventriosum*, *Ruminococcus bromii*, and *Ruminococcus obeum* were significantly associated with obese subjects [23]. A cross-sectional study in Japan re-

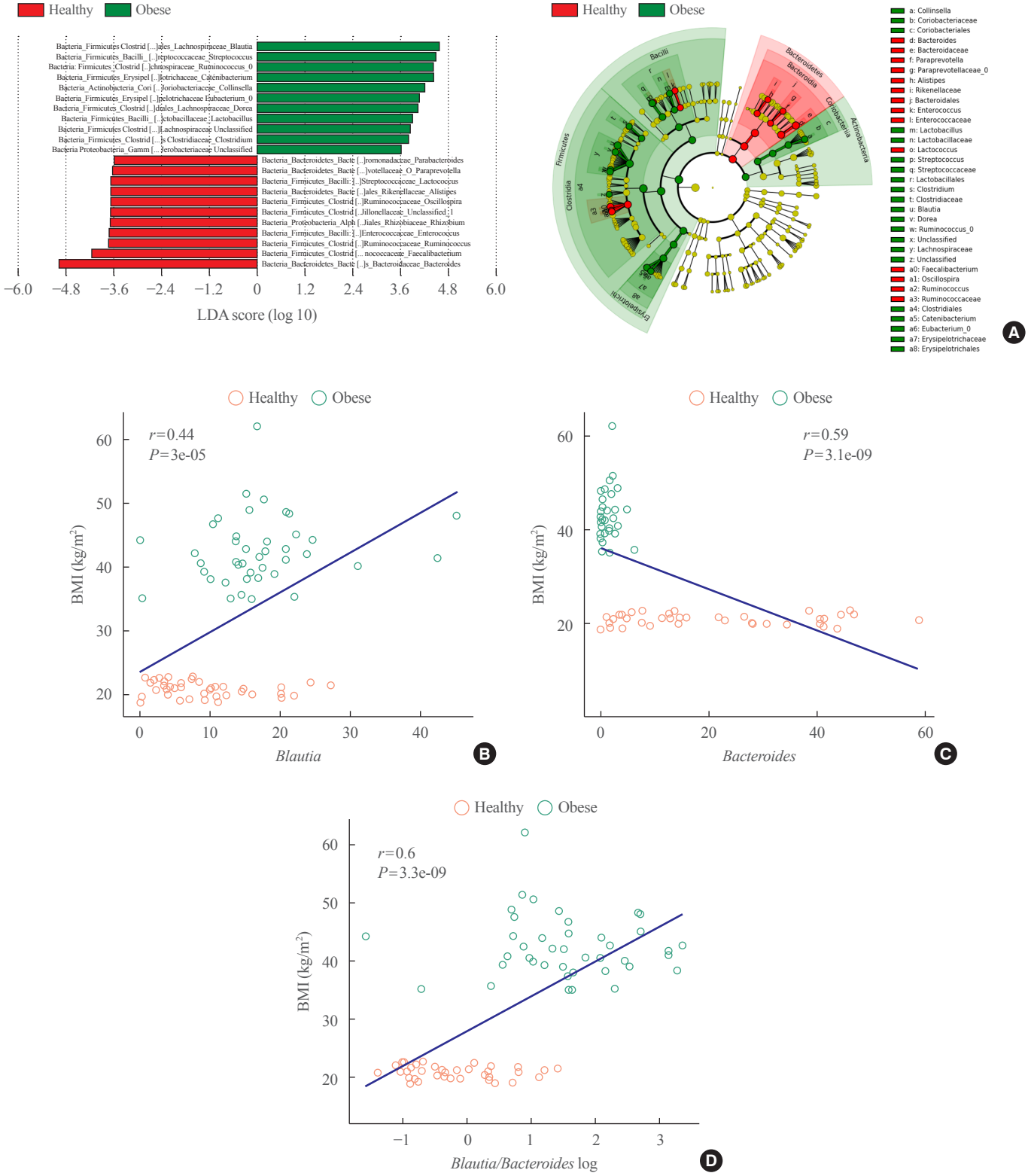

Fig. 5. Prominent gut microbiota between severe obese patients and healthy controls and correlation with body mass index (BMI). (A) Linear discriminant analysis (LDA) effect size between severely obese patients and healthy controls (left panel). Cladogram analysis between severely obese patients and healthy controls (right panel). (B) Correlation between *Blautia* and BMI. (C) Correlation between *Bacteroides* and BMI. (D) Correlation between the log value of *Blautia*/*Bacteroides* and BMI.

ported that *Blautia* was the only genus whose abundance showed a significant negative relationship with visceral fat accumulation in Japanese people regardless of sex [24]. A study for a Chinese population presented that *Blautia wexlerae* and *Bacteroides dorei* were the strongest predictors for weight loss when present in high abundance at baseline [25]. *Blautia* is a taxonomic genus placed in the *Lachnospiraceae* family of the *Firmicutes* phylum. *Blautia* are anaerobic bacteria with the ability to ferment different carbohydrates and are a common acetic acid producer in the intestine, which may inhibit insulin signaling and fat accumulation in adipocytes [26]. Despite the increasing level of knowledge about *Blautia*, it is still poorly understood, therefore further studies are needed to cement the role of *Blautia*.

Regarding the effect of bariatric surgery type on the microbiota profile, several studies found that both LSG and LRYGB resulted in an increase of diversity index and gene richness of gut microbiota, and in parallel with weight loss, another study reported that LRYGB induces greater taxonomic and functional changes in gut microbiota than LSG [27]. Conversely, another study reported no significant differences between surgery types [28]. Following LRYGB, the nutrient-stimulated circulating levels of the gut hormones peptide YY and glucagon-like peptide 1 are markedly elevated as a consequence of increased L cells, which result from the anatomical rearrangement. Thus, these changes might occur more in LRYGB than LSG [29]. Our study shows that the log value of the *Blautia*/*Bacteroides* ratio showed a positive correlation with BMI, regardless surgery type.

To validate the correlation between specific microbiomes and BMI, we examined the microbial relationship between patients with severe obesity and healthy volunteers with normal BMI. Similar to the results of bariatric surgery, the microbiomes of severe obese patients differed in diversity from those of healthy person with more enriched Firmicutes and deficient Bacteroidetes at the phylum level and more abundant *Blautia* and deficient *Bacteroides* at the genus level. Moreover, we found that the log value of the *Blautia*/*Bacteroides* ratio had a positive correlation with BMI. As mentioned above, the physiological effects of *Blautia* in obesity is controversial. The strength of our study is that the results acquired by analyzing fecal samples before and after bariatric surgery were re-confirmed by the validation comparing fecal samples of severely obese patients and healthy volunteers. However, our study has several limitations. First, we did not re-collect fecal samples after bariatric surgery from all 58 patients who provided their fecal samples at the baseline, therefore we only assessed the data of 22 patients (37.9%) of the initially enrolled 58 patients. Second, further basic experiments to investigate the role of *Blautia* and *Bacteroides* in obesity have not been conducted in this study. In the next step, we plan to perform both *in vitro* and *in vivo* experiments to cement our results. Third, this study was carried out for obese patients who underwent bariatric surgery in a single institution. Therefore, these results may not be representative of populations from other institutions and countries. Further studies for large population are needed to corroborate our results. Fourth, we did not investigate the change in dietary habits after bariatric surgery, therefore we could not confirm that the observed changes in the *Blautia*/*Bacteroides* ratio after bariatric surgery are caused by the surgery itself or a change in dietary habits after surgery. This issue will have to be addressed in further studies.

In summary, we identified that the *Blautia*/*Bacteroides* ratio had a positive correlation with BMI in the gut microbial analysis of patients who underwent bariatric surgery and verified these results by performing a validation study for patients with severe obesity and healthy volunteers with normal BMI. The altered *Blautia*/*Bacteroides* ratio after bariatric surgery suggests that bariatric surgery could change the taxonomy composition of the gut microbiota, and that specific microbiomes including *Blautia* and *Bacteroides* might have a potential role in obesity.

CONFLICTS OF INTEREST

This study was sponsored by Cell Biotech Co. Ltd. Jae Hyun Kim is a consultant to Cell Biotech Co. Ltd. and has received grant support from Cell Biotech Co. Ltd. Dooheon Son and Sanghyun Lim are employees of Cell Biotech Co. Ltd. Yoonhong Kim, Bu Kyung Kim, Ki Hyun Kim, Kyung Won Seo, Kyoungwon Jung, and Seun Ja Park have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conception or design: B.K.K., K.W.S., S.L., J.H.K.
Acquisition, analysis, or interpretation of data: Y.K., D.S., K.H.K., K.J., S.J.P.
Drafting the work or revising: Y.K., D.S., S.L., J.H.K.
Final approval of the manuscript: Y.K., D.S., B.K.K., K.H.K., K.W.S., K.J., S.J.P., S.L., J.H.K.

ORCID

Yoonhong Kim *https://orcid.org/0000-0003-1611-5390*
Dooheon Son *https://orcid.org/0000-0003-0930-1494*

Sanghyun Lim *https://orcid.org/0000-0003-3422-3766*
Jae Hyun Kim *https://orcid.org/0000-0002-4272-8003*

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