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CLINICAL TRIAL REPORT

Pharmacokinetic and Pharmacodynamic Interaction of Metformin and Ojeok-san in Healthy Volunteers

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Purpose: This study aimed to evaluate the pharmacokinetics and pharmacodynamics of metformin and Ojeok-san (OJS) co-administration to healthy volunteers compared to those with metformin alone.

Methods: This was an open-label, one-sequence, crossover study, with two 2-day hospitalization schedules lasting up to 14 days. Metformin was administered once daily on days 1 and 2. OJS was administered alone three times a day on days 3–7 and co-administered with metformin once a day on days 8 and 9. Plasma concentrations of metformin were measured using a validated LC-MS/MS method. To evaluate pharmacodynamics, oral glucose tolerance tests (OGTTs) were performed on days 1, 2, 8 and 9.

Results: Fifteen participants were enrolled. The coadministration decreased C_{max} (1757.7 to 1668.9 ng/mL) and AUC_{last} (10407.4 to 9901.1 ng·h/mL), compared to those with metformin alone. Geometric mean ratios (90% Confidence Interval) of C_{max} and AUC_{last} between the co-administration with OJS and metformin alone were 92.15% (82.79–102.57) and 94.57% (85.6–104.48), respectively. Co-administration with OJS did not significantly change the mean glucose level compared to that with metformin alone.

Conclusion: Co-administration with OJS decreased the plasma concentrations of metformin compared to that with metformin alone. However, the degree of decrease was not significant based on the geometric mean of the C_{max} and AUC_{last}. Considering the OGTT results, these changes in metformin concentration did not affect glucose concentration. In addition, there were no significant findings regarding safety profiles.

Keywords: metformin, ojeok-san, drug-herb interaction, pharmacokinetics, pharmacodynamics

Introduction

Type 2 diabetes mellitus (DM) is a chronic disease in which blood sugar levels are elevated due to an abnormal response of beta cells to insulin activity.[1,2] It leads to microvascular and macrovascular complications, which are major problems associated with morbidity and mortality in patients with type 2 DM.[3] Microvascular complications include retinopathy, neuropathy, and nephropathy, whereas macrovascular complications include coronary artery disease, cerebrovascular disease, peripheral artery disease, and heart failure. These complications cause significant psychological and physical suffering in patients and place a substantial burden on public health systems.[1,4] The prevalence of diabetes was reported to be 13.9% in 2020 in Korea and 11.6% in 2021 in the United States.[5,6] Considering the numerous patients, diabetes is a major disease requiring long-term public health management.

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To control blood glucose levels, patients with diabetes should take hypoglycemic agents regularly and consistently. Among these drugs, metformin is the first-line medication prescribed to patients with type 2 DM because it can effectively manage glucose levels and has a favorable safety profiles.[7] Furthermore, clinical evidence indicates that metformin reduces the incidence of cardiovascular events in patients with diabetes.[8]

Individuals with type 2 DM may take other hypoglycemic drugs or medications along with metformin for various medical reasons. Therefore, there have been continuous reports on drug interactions following the concomitant administration of metformin and other drugs.[9] Interactions between metformin and other drugs must be evaluated in terms of their pharmacokinetics and pharmacodynamics. Metformin is excreted in an unchanged form in urine without metabolism and widely distributed in the body by organic cation transporters (OCTs).[10] Therefore, the pharmacokinetics of these drug transporters must be evaluated. Metformin lowers blood glucose levels by suppressing hepatic glucose production and facilitating glucose uptake in peripheral tissues, and these pharmacological effects can be affected by other drugs.[9,11] Additionally, alterations in the pharmacokinetics and pharmacodynamics of metformin are possible because of its interaction with herbal drugs rather than chemical drugs.[12]

Ojeok-san (OJS) is one of most widely used herbal medicines in Korea, reported to account for the highest percentage (18.6%) of the total insurance claims for mixed herbal medicine prescriptions.[13] OJS is consists of 17 medicinal herbs.[14] It is used to control gastrointestinal and gynecological symptoms and various types of pain, such as arthritis, back pain, and headaches. Taking OJS for these various reasons means that patients with type 2 DM are more likely to take metformin along with OJS. Plasma concentrations of metformin could be increased or decreased when metformin and OJS are co-administered. This is because any of the 17 medicinal herbs in OJS can act as substrates, inhibitors, or inducers of OCTs.

Metformin is not metabolized and is excreted directly in urine.[10] Therefore, an evaluation of the absorption and excretion of metformin is required. Plasma membrane monoamine transporter (PMAT) and OCT1 play important roles in intestinal absorption.[15] The hepatic uptake of metformin is mainly mediated by OCT1 and may also be mediated by OCT3.[16,17] Metformin transfer from circulation into renal epithelial cells is facilitated by OCT2, and renal excretion of metformin into the lumen is mediated by human multidrug and toxin extrusion 1 (MATE1) and MATE2-K.[9,10] Metformin and OJS interactions were evaluated through the inhibition of metformin transporters (OCTs and MATEs). Relevant in vitro or in vivo studies on transporters in OJS to design this clinical trial were not found.

If blood glucose is not adequately controlled by the co-administration of metformin and OJS, OJS should be replaced with other herbal medicines or drugs. These herb-drug interactions require quantitative evaluation of changes in the pharmacokinetics and pharmacodynamics of metformin through prospective clinical trials administering metformin alone or metformin plus OJS to healthy volunteers. Therefore, this study aimed to evaluate the pharmacokinetics and pharmacodynamics of metformin, alone and in combination with OJS, in healthy volunteers.

Materials and Methods

Participants

Healthy male participants, 19 to 45 years old, with a body mass index of 18.0 to 29.0 kg/m^2 were enrolled in this study. Participants provided written informed consent after receiving a detailed explanation of the study and were screened for eligibility. The screening assessment included medical history, physical examination, 12-lead electrocardiography, and clinical laboratory tests. The study protocol and informed consent forms were approved by the Korean Ministry of Food and Drug Safety, Institutional Review Board (IRB; IRB number: KHUH 2021-05-007) of Kyung Hee University Hospital (KHUH, Seoul, Republic of Korea), and IRB (IRB number: KOMCIRB 2021-06-004) of Kyung Hee University Korean Medical Hospital (KHUKMH, Seoul, Republic of Korea).

Design

This open-label, single-sequence, crossover clinical study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice (Clinical Research Information Service, CRIS [https://cris.nih.go.kr]; registry number: KCT0006799).

The study included two 2-day hospitalization schedules that lasted up to 14 days, excluding the screening schedule (Figure 1 and Supplementary Table 1). In the first period (days 1–2), all participants enrolled in the screening evaluation were hospitalized on the morning of day 1 and discharged on the evening of day 2. In the second period, patients were hospitalized and discharged over the same amount of time on days 8–9. Metformin was administered once daily on days 1 and 2. In the second period (days 3–10), OJS was administered alone on days 3–7 and co-administered with metformin once daily on days 8–9. The 1000 mg metformin tablet was orally administered once daily at approximately 1 PM on days 1 and 8 and approximately 8 AM on days 2 and 9. The 4.35 g/pack OJS was orally administered thrice daily at approximately 7–10AM, 12–3 PM, and 6–9 PM on days 4–9. (The 4.35 g/pack OJS was orally administered thrice daily, approximately 6 h apart, from morning to night on days 4–9). When metformin and OJS were co-administered on the morning of days 8 and 9 of hospitalization, OJS was administered 1 h earlier than metformin. All the participants received standard meals during hospitalization.

For the pharmacokinetic analysis of metformin, blood samples were collected before every drug administration on days 1, 2, 8, and 9. On days 2 and 9, steady-state blood samples were sequentially collected before metformin administration (0 h) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 h after administration.

For pharmacodynamic analysis, all the oral glucose tolerance tests (OGTTs) were conducted for 3 h. The OGTTs on days 1 and 8 were conducted from 10 AM to 1 PM, just before the administration of metformin, and those on days 2 and 9 were conducted from 2 to 5 h after the administration of metformin. The start time for all OGTTs was approximately 10 AM. For the OGTT, glucose (75 g) was orally administered, and blood samples were collected before (0 h) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, and 3 h after glucose intake. All participants were required to fast for 8 h before the OGTT.

All participants were discharged on the morning of day 10. The clinical study was completed after evaluating the safety profile through an outpatient visit (post-study visit) on one day from days 11 to 14.

Determination of Metformin Concentration

Plasma metformin concentrations were estimated using LC-MS/MS with an API 2000 triple quadrupole mass spectrometer (ABSciex, Framingham, MA, USA) coupled with an Agilent 1100 series HPLC system (Agilent Technologies, Waldronn, Germany). Metformin and metformin-d6 (IS) were separated using a Gemini® C18 column (50 × 2.0 mm, 3 µm; Phenomenex, USA) at 40 °C. The mobile phase consisted of 10 mM ammonium formate (pH 3.2) and 100% acetonitrile (80:20, v/v) with a flow rate of 150 µL/min. The compounds were detected in positive mode using an electrospray ionization source. The mass spectrometer was operated in multiple reaction monitoring mode with a mass-to-charge ratio (m/z) of 129.93 → 71.10 for metformin and 136.90 → 77.10 for IS. Samples were extracted using protein

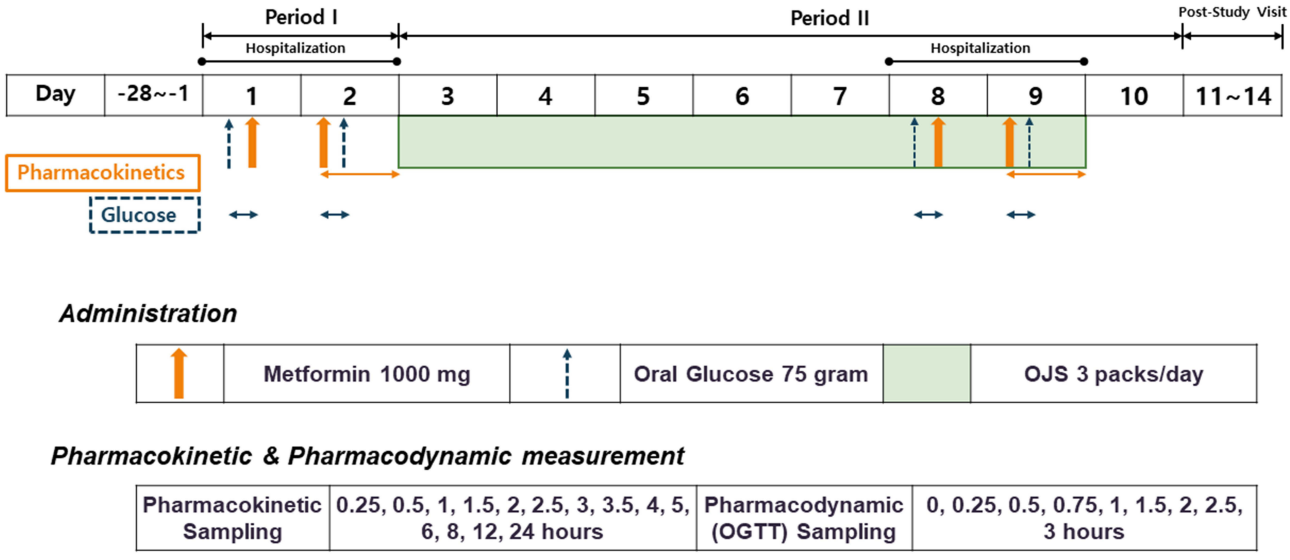

Figure 1 Schedule of the clinical study.

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precipitation using acetonitrile. The injection volume was 7 μL. Metformin showed a linear response in the range of 50–5000 ng/mL ($r^2 \geq 0.9940$) and the lower limit of quantification was determined as 50 ng/mL with S/N ratio ≥ 14.1. The intra- and inter-day precisions for metformin were less than 4.64% and 6.83%, respectively. The intra- and inter-day accuracies for metformin were less than 8.94% and 6.33%, respectively.

Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic parameters were calculated using the noncompartmental method in Phoenix™ WinNonlin® 8.3 (Certara USA Inc., Princeton, NJ, USA). The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were directly determined using individually observed concentration-time profiles. The terminal elimination rate constant (kz) was obtained from the regression line of the log-linear decrease in the plasma concentration-time profile, and the terminal elimination half-life ($t_{1/2}$) was calculated from the natural logarithm of 2 divided by kz. The area under the plasma concentration-time curve (AUC) from the time of second dose of metformin to the last measurable time point (AUC_{last}) was calculated using the linear/log trapezoidal rule. The AUC from the time second dosing to infinity (AUC_{inf}) was calculated as the sum of the AUC_{last} and the extrapolated area, which was the last measurable concentration divided by kz. The apparent clearance (CL/F) was calculated as the metformin dose divided by the AUC_{inf}.

Pharmacodynamic parameters were also calculated using the noncompartmental method in Phoenix™ WinNonlin® 8.3. The maximum serum glucose concentration (G_{max}) and 2-h post-OGTT glucose levels (PP2) were obtained from individual glucose concentration-time profiles. The area under the glucose concentration-time curve for 3 h after glucose administration ($AUG_{0\text{-}3h}$) was calculated using the linear trapezoidal rule. To assess the glucose-lowering effect of metformin for each period, the change and percent change (%change) were derived from the OGTT performed before metformin administration (days 1 and 8) to that performed after administration (days 2 and 9) as follows changes of G_{max}, $AUG_{0\text{-}3h}$, and PP2 were calculated as changes between Day 2 and Day 1 (="Day2 - Day1") and between Day 9 and Day 8 (="Day9 - Day8"). The %changes were calculated as changes divided by those on Day 1 or 8, ie "100×(Day2 - Day1)/Day1" or "100×(Day9 - Day8)/Day8".

Safety and Tolerability Assessment

Safety and tolerability were assessed during the study period. The occurrence of adverse events (AEs) was monitored and investigators assessed their causal relationship with metformin or OJS. Vital signs, 12-lead electrocardiogram, physical examinations, and clinical laboratory tests were performed and reviewed. Changes from baseline with respect to these results were considered in the tolerability assessment.

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, NC, USA). Descriptive statistics (eg, arithmetic means, standard deviations, and ranges) for continuous variables were calculated. The pharmacokinetic parameters, C_{max}, AUC_{last}, and AUC_{inf}, were converted into logarithmic forms and compared between period 1 (metformin alone) and period 2 (metformin with OJS) using the paired *t*-test. These comparisons were calculated as geometric mean (GMR) ratios (%) with 90% confidence intervals (CI), assessed using a conventional bioequivalence range of 80–125%. The pharmacodynamic parameters, G_{max}, $AUG_{0\text{-}3h}$, and PP2, were expressed as absolute and percentage changes, and compared using a paired *t*-test. The results were summarized as the mean difference with 95% CI. Scatter plots of both pharmacokinetic and pharmacodynamic parameters were reviewed to visually represent the data, and the coefficient of determination (R^2) from a linear regression model was calculated to evaluate their association. All figures were visualized using the ggplot2 package in the R program (version 4.4.2).[18,19]

Results

Demographic Characteristics

Fifteen participants were enrolled in the study. All participants completed the study without withdrawing, and were included in the pharmacokinetic and pharmacodynamic analyses. The mean (standard deviation, ranges) of age, weight,

height, and body mass index for the 15 participants was 26.47 (2.97, 22–32) years, 71.45 (9.65, 58.3–88.8) kg, 177.18 (6.15, 165.8–191.2) cm, and 22.71 (2.28, 18.32–26.68) kg/m^2, respectively.

Pharmacokinetic Characteristics

The mean concentrations of metformin decreased with co-administration, compared to that with metformin alone (Figure 2). Metformin and OJS co-administration delayed median T_{max} by 0.5 h, compared to that with metformin alone (Table 1). The co-administration decreased C_{max} (1757.7 to 1668.9 ng/mL) and AUC_{last} (10407.4 to 9901.1 ng·h/mL), compared to those with metformin alone. Geometric mean ratios (90% CI) of C_{max} and AUC_{last} between metformin with OJS and metformin alone were 92.15% (82.79–102.57) and 94.57% (85.6–104.48), respectively (Table 1). In addition, in two-thirds of all participants, the co-administration of metformin and OJS reduced the C_{max} and AUC_{last} compared to those with metformin alone (Figure 3).

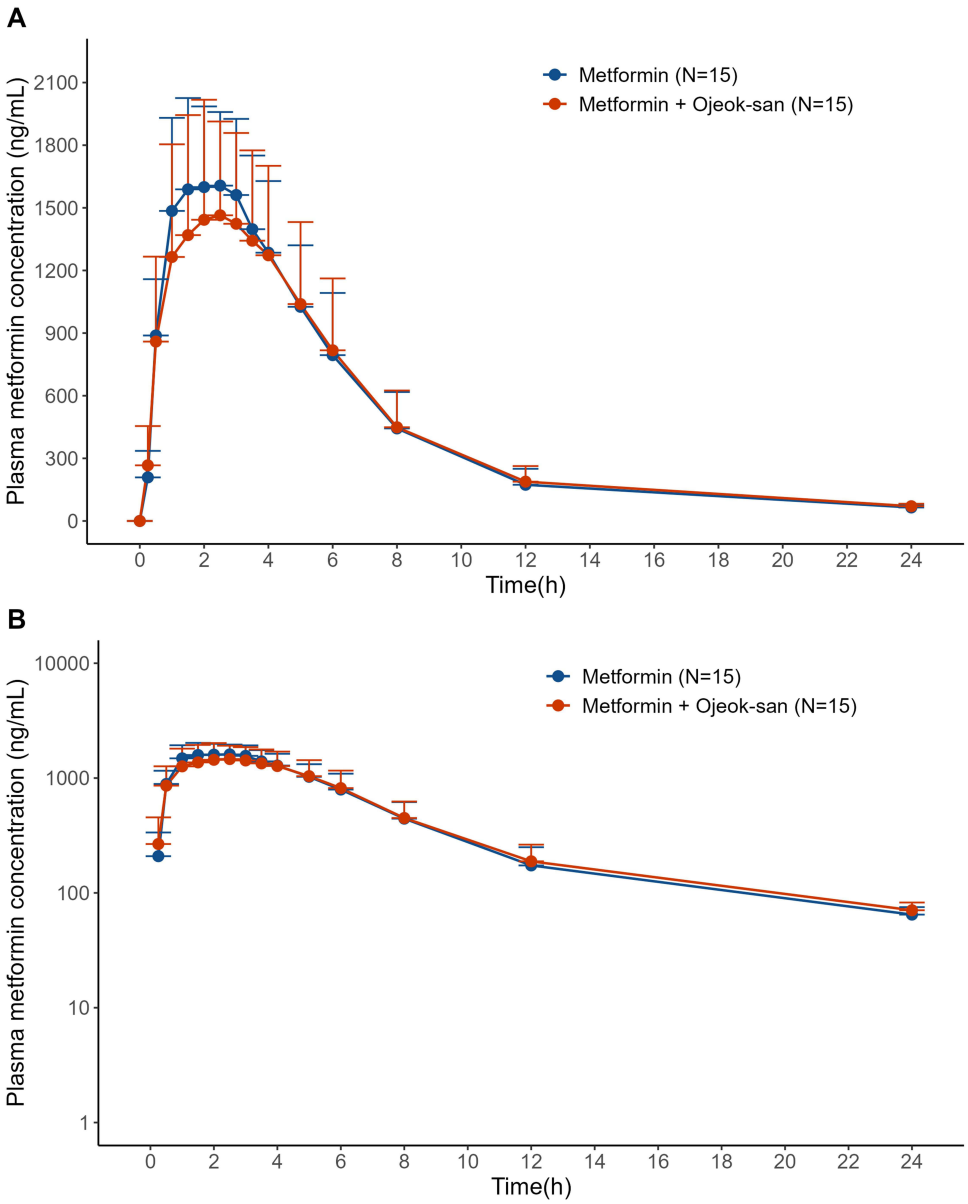

Figure 2 Mean concentration-time curves of metformin after the administration of metformin alone or coadministration of metformin with Ojeok-san in (**A**) linear and (**B**) logarithmic scale. The error bar indicates the standard deviation.

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Table 1 Comparisons of Pharmacokinetic Parameters of Metformin When Administration of Metformin and Ojeok-San Compared to Those with Administration of Metformin Alone

Parameter	Metformin (n=15)	Metformin + Ojeok-San (n=15)	Geometric Mean Ratio (%, 90% CI)[a]
T_{max} (h)	2.5 (1.0–4.0)	3.0 (1.0–5.0)	
C_{max} (ng/mL)	1757.66 ± 424.46	1668.87 ± 606.54	92.15 (82.79–102.57)
AUC_{last} (ng·h/mL)	10407.39 ± 3021.23	9901.14 ± 3009.21	94.57 (85.60–104.48)
AUC_{inf} (ng·h/mL)	10927.43 ± 3067.01	10,503.13 ± 3067.01	95.69 (86.78–105.52)
AUC_{extra} (%)	4.95 ± 2.05	6.05 ± 2.63	
$t_{1/2}$ (h)	3.68 ± 1.42	3.50 ± 1.27	
CL/F (L/h)	99.79 ± 35.10	104.53 ± 35.40	

Notes: [a]The geometric mean ratio and the 90% confidence interval were calculated using a paired *t*-test.
Abbreviations: T_{max}, time to reach maximum concentration; C_{max}, maximum concentration; AUC_{last}, area under the curve from time zero to the last measurable concentration; AUC_{inf}, area under the curve from time zero to infinity; AUC_{extra}, area under the curve from the last measurable concentration to infinity; $t_{1/2}$, half-life; CL/F, clearance after oral administration; CI, confidence interval.

Pharmacodynamic Characteristics

The mean glucose concentrations were compared before and after metformin administration on days 1–2 and 8–9 (Figure 4). There were no significant differences in individual glucose levels at each time point (before and after treatment) between metformin alone and co-administration with OJS (Figure 4). There were also no marked changes or %changes in glucose levels between metformin alone and co-administration with OJS (Figure 5). Changes or %changes in G_{max}, $AUG_{0\text{-}3h}$, and PP2 were not significantly different between metformin alone and co-administration with OJS (Table 2).

Pharmacokinetic and Pharmacodynamic Relationships

Individual changes or %changes in G_{max}, $AUG_{0\text{-}3h}$, and PP2 are displayed according to the C_{max} or $AUC_{0\text{-}8h}$ of metformin between metformin alone and co-administration with OJS (Supplementary Figures 1 and 2). Although co-administration with OJS resulted in modest mean changes in the pharmacokinetic and pharmacodynamic parameters compared to metformin alone, no clinically meaningful correlations were observed between pharmacokinetic and pharmacodynamic findings (Supplementary Figures 3 and 4). Specifically, the differences in the changes of G_{max}, $AUG_{0\text{-}3h}$, and PP2 were not consistently associated with the individual ratios of metformin C_{max} or $AUC_{0\text{-}8h}$, as indicated by the low R^2 values in all comparisons. No clinically relevant pharmacokinetic-pharmacodynamic relationship was observed in either metformin alone or co-administration with OJS.

Safety Profiles and Tolerability

Among the 15 participants, seven (46.7%) in period 1 and nine (60.0%) in period 2 reported AEs. All AEs were evaluated as being related to the administration of metformin or OJS, except for one AE reported in period 2. The AEs were diarrhea (seven cases in period 1 and eight in period 2) and abdominal discomfort (one in period 2). The AEs in period 1 were considered to be associated with metformin and those in period 2 were considered to be associated with metformin or OJS. None of the participants withdrew from the study because of AEs. Safety profiles and tolerability assessments, including vital signs, physical examination, and clinical laboratory tests, showed no significant results or changes from baseline assessments. In particular, no significant increase was observed in liver function-related parameters, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Supplementary Figure 5).

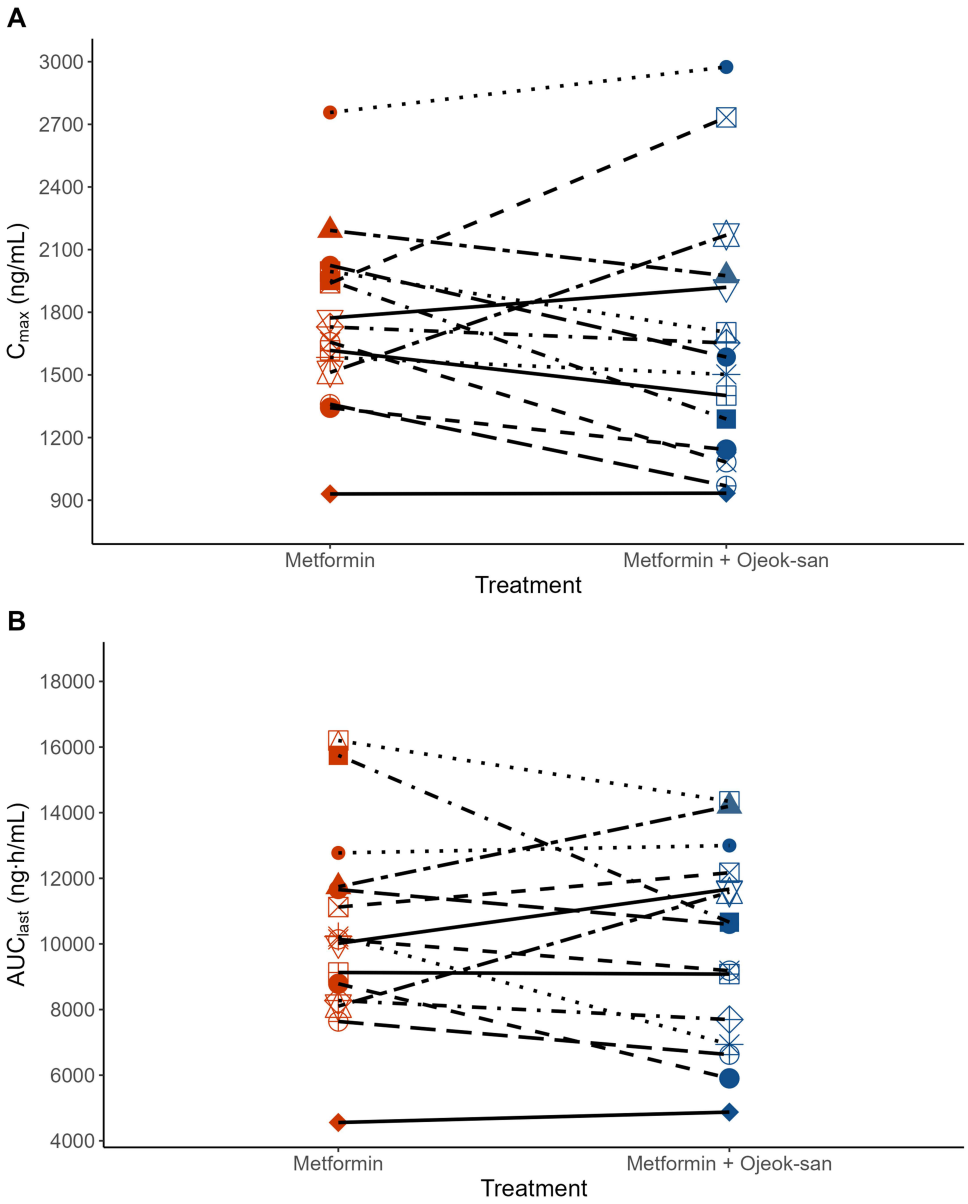

Figure 3 Individual values of (**A**) C_{max} and (**B**) AUC_{last} of metformin after the administration of metformin alone and coadministration of metformin and Ojeok-san.
Note: Each symbol connected by a line represents an individual participant and the changes observed across treatment conditions. Colors indicate the treatment condition: Metformin versus Metformin + Ojeok-san.
Abbreviations: C_{max}, maximum concentration; AUC_{last}, area under the curve from time zero to last measurable concentration.

Discussion

Metformin is excreted unchanged in urine, requiring an evaluation of its absorption and excretion when co-administered with OJS.[10] Its transport involves PMAT, OCTs, and MATEs.[15–17] The interaction with OJS was assessed based on potential transporter inhibition, but no relevant in vitro or in vivo studies were found. Although OJS has not been directly studied, a similar pharmacokinetic pattern was observed in a clinical study that investigated the interaction between metformin and another herbal medicine, goldenseal.[20] In that study, there was a noted decrease in metformin's AUC without a significant change in its half-life. This effect was attributed to mechanisms involving the inhibition or induction of OCTs, which may also apply to the current study. Nevertheless, considering the quantitative pharmacokinetic results of the current study, it was concluded that the effect of OJS on the transporter is minimal.

Metformin was administered once daily for two consecutive days in each period. It was concluded that it would be possible to evaluate drug interactions with OJS even after taking metformin for 1 to 2 days, because the half-life of metformin is reported to be

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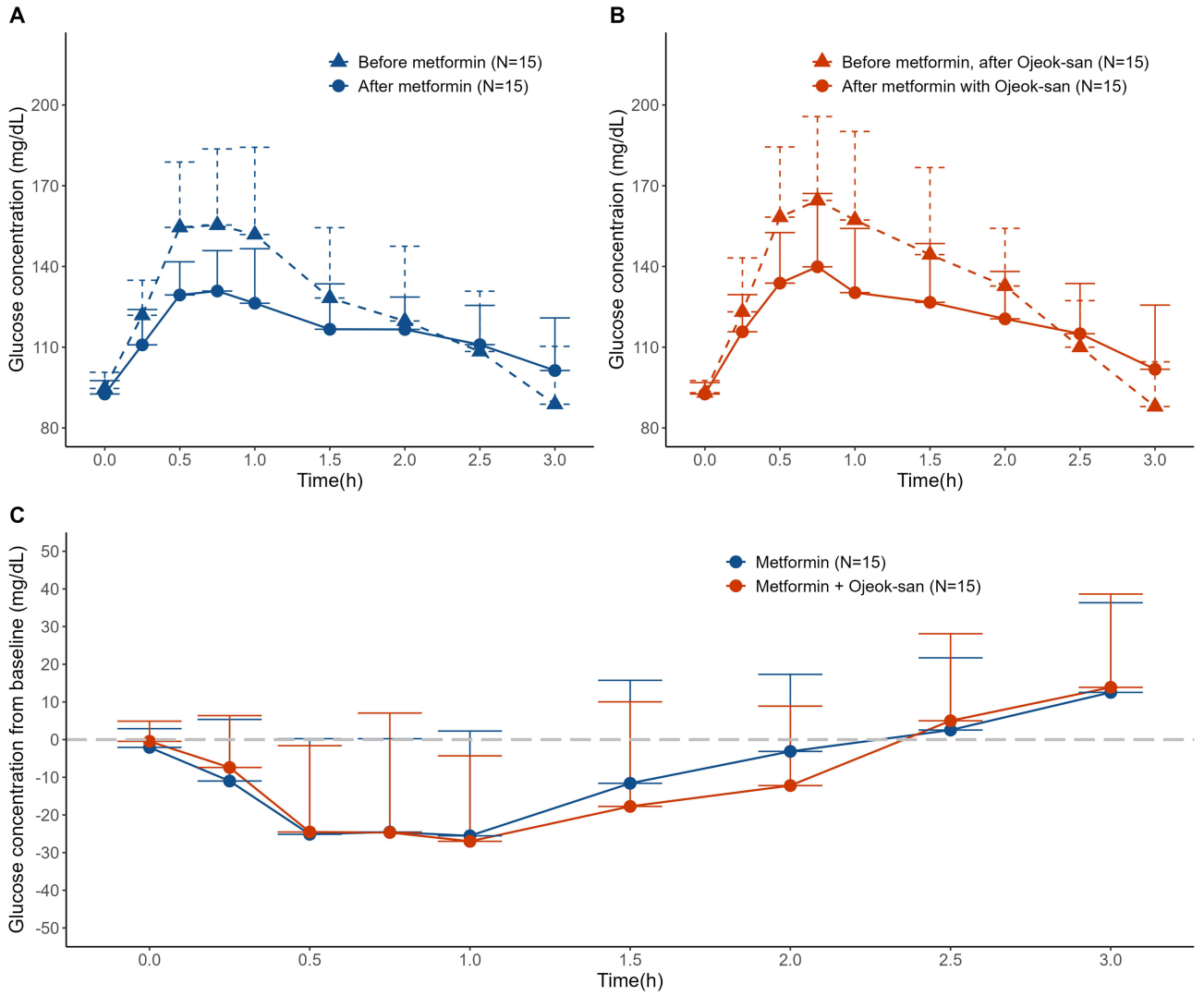

Figure 4 Mean concentration-time curves of glucose after oral glucose tolerance tests (OGTTs) (**A**) before and after metformin administration on days 1 and 2, (**B**) after Ojeok-san administration, before metformin administration, and after coadministration of metformin and Ojeok-san on days 8 and 9. (**C**) Changes in glucose concentration before and after metformin administration during OGTT, calculated as "day 2 - day 1" and "day 9 - day 8". The error bar indicates the standard deviation.

1.52 to 5.1 h.[21,22] In the current study, the mean terminal half-life was 3.50 and 3.68 h. In addition, because the metformin concentrations at 0 h before the metformin administration on the days 2 or 9 were less than 5% of C_{max} in all the participants, except for two participants in period 2, there may be little drug accumulation regarding pharmacokinetics when taking 1000 mg of metformin once daily.

In a previous study on OGTTs using 75 g of glucose in healthy Korean participants (N=34), the mean $AUG_{0\text{-}3h}$/PP2 value (SD) before dosing was 384 (65.9) mg·h/dL/120.2 (33.9) mg/dL.[23] In another study evaluating OGTTs using 75 g glucose in healthy participants, two median $AUG_{0\text{-}3h}$/PP2 values (interquartile ranges, IQR) at pre-dose were 391.2 (19.8) mg·h/dL/132.5 (19.0) mg/dL (N=10) and 397.8 (67.8) mg·h/dL/139.0 (38.0) mg/dL (N=10).[22] In this previous study, OGTT was performed at 2 h after the dose of metformin 1000 mg, and the median $AUG_{0\text{-}3h}$/PP2 value (IQR) at post-dose was 370.3 (39.6) mg·h/dL/125.5 (31.0) mg/dL. The median value of individual $AUG_{0\text{-}3h}$/PP2 differences (reduction) between post-dose and pre-dose values was 41.9 (60.1) mg·h/dL/16.5 (22.0) mg/dL. These differences were comparable with the results of the current study; median value (IQR) of individual $AUG_{0\text{-}3h}$/PP2 reductions was 23.63 (43.75) mg·h/dL/0 (21) mg/dL at period 1 (metformin alone) and 39.13 (37.38)/10 (24.5) at period 2 (OJS coadministration). Comparing the $AUC_{0\text{-}3h}$ or PP2 reductions in the previous study and those in the current study, the differences in $AUC_{0\text{-}3h}$/PP2 changes between the two periods were not clinically significant.

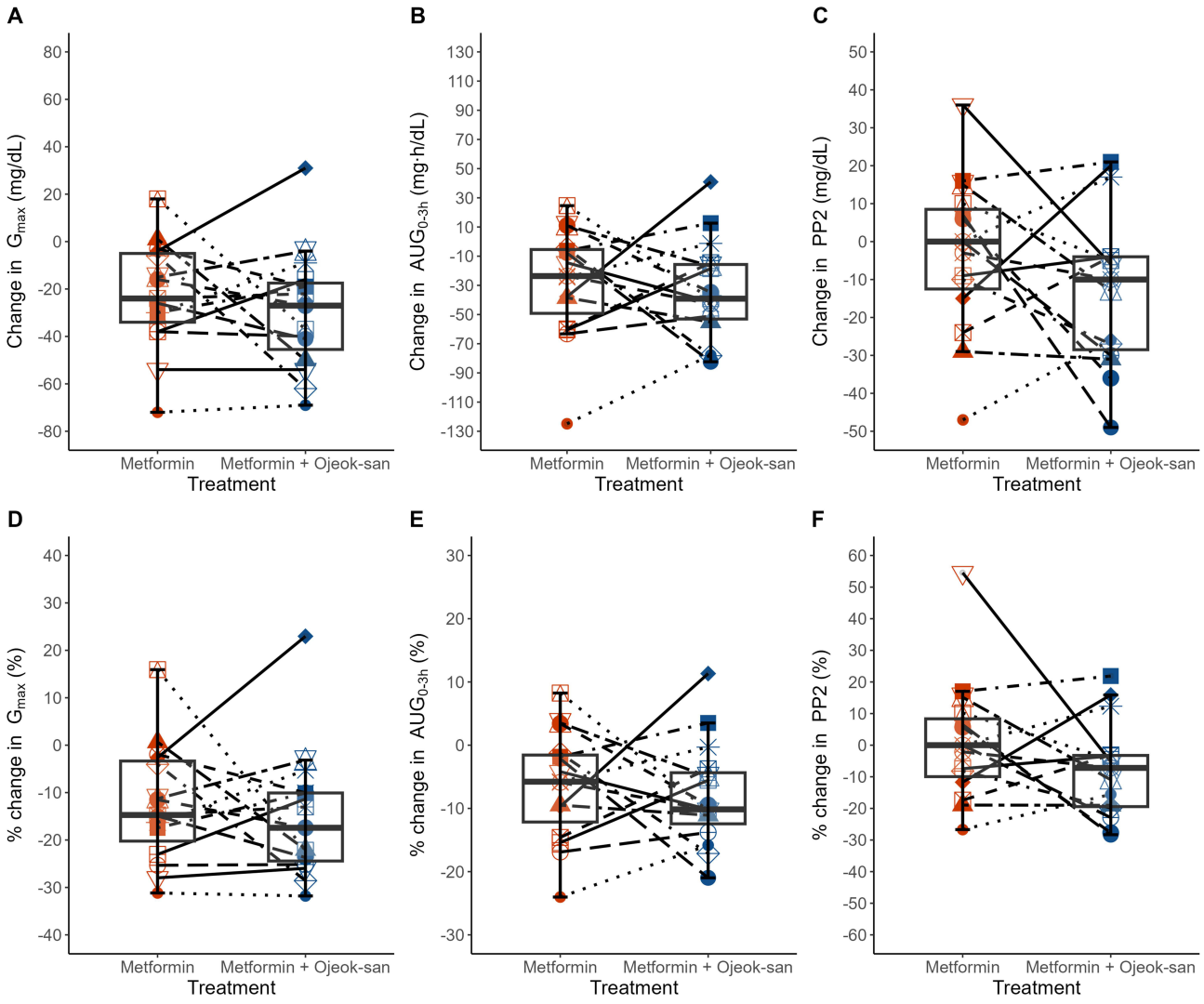

Figure 5 Individual changes and %changes of glucose (**A** and **D**) G_{max}, (**B** and **E**) $AUG_{0\text{-}3h}$, (**C** and **F**) PP2.
Note: Box plots represent the median and interquartile range. Each symbol connected by a line represents an individual participant and the changes observed across treatment conditions. Colors indicate the treatment condition: Metformin versus Metformin + Ojeok-san.
Abbreviations: G_{max}, maximum glucose concentration; $AUG_{0\text{-}3h}$, area under the glucose concentration-time curve from 0 to 3 h; PP2, 2-h post-OGTT glucose level.

In the clinical study for the repeated OGTTs using 75 g of glucose (N=8), changes of glucose $AUG_{0\text{-}120min}$ for each repeated glucose measurement during 3 days were reported as −3.7 to 47.4 mmol/L·120/min (−1.11 to 14.23 mg·h/dL).[24] Therefore, mean $AUG_{0\text{-}3h}$(SD) difference before dosing between periods 1 and 2, ie "377.13(54.75) mg·h/dL" versus "397.66(50.26) mg·h/dL" can be regarded as inter-day variability of glucose, although OJS administered 3 h before glucose dosing at period 2 could increase glucose levels. Meanwhile, the difference in PP2 changes between both periods was marked, especially regarding glucose changes from 1.5 to 2 h (Figure 4). These findings could be interpreted as the result of glucose levels at 1.5 and 2 h before dosing (on day 8) in period 2 being higher than those (on day 1) in period 1.

The AEs in the current study were diarrhea (seven cases in period 1 and eight cases in period 2) and abdominal discomfort (one case in period 2), which have been reported following the administration of metformin in previous studies.[25] These AEs were not reported during OJS administration alone on days 3–7. Therefore, we concluded that the AEs in period 2 were related to metformin rather than to OJS. OJS has the potential to increase ALT or AST levels when administered repeatedly. No increasing trends in ALT or AST levels were found in any of the participants, although one participant's ALT level was above the reference range during the screening period (Supplementary Figure 5).

In this study, the co-administration of metformin and OJS led to an approximately 5% decrease in the AUC of metformin. This reduction is not considered clinically significant according to the FDA's criteria for assessing drug-drug

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Table 2 Comparisons of Oral Glucose Tolerance Test (OGTT) Results Before and After Administration of Metformin or Metformin and Ojeok-San

Parameter	Metformin (n=15)		Metformin + Ojeok-San (n=15)		Difference[a]
	Before	After	Before	After	Mean (95% CI)
G_{max} (mg/dL)	161.60 ± 27.79	139.13 ± 14.16	176.13 ± 31.06	146.93 ± 19.46	
Change (mg/dL)	−22.47 ± 22.89		−29.20 ± 25.54		−6.73 (−22.32, 8.85)
%change (%)	−12.38 ± 12.47		−15.12 ± 13.66		−2.74 (−11.70, 6.23)
AUG_{0-3h} (mg·h/dL)	377.13 ± 54.75	349.17 ± 26.60	397.66 ± 50.26	364.33 ± 40.38	
Change (mg·h/dL)	−27.97 ± 38.12		−33.33 ± 34.71		−5.37 (−31.88, 21.15)
%change (%)	−6.40 ± 8.74		−7.91 ± 8.33		−1.51 (−8.14, 5.12)
PP2 (mg/dL)	119.73 ± 27.78	116.60 ± 12.03	132.73 ± 21.42	120.53 ± 17.61	
Change (mg/dL)	−3.13 ± 20.45		−12.20 ± 21.08		−9.07 (−21.27, 3.14)
%change (%)	1.11 ± 19.45		−7.84 ± 15.33		−8.95 (−19.52, 1.62)

Notes: [a]The mean difference and the 95% confidence interval were calculated using a paired *t*-test.
Abbreviations: G_{max}, maximum glucose concentration; AUG_{0-3h}, area under the glucose concentration-time curve from 0 to 3 h; PP2, 2-hpost-OGTT glucose level; CI, confidence interval.

interactions and does not necessitate a dose adjustment.[26] Additionally, although a decrease in AUC and C_{max} was observed, the OGTT results indicated a trend toward lower average blood glucose levels in the coadministration of metformin with OJS, even though this trend did not reach statistical significance. These small and statistically non-significant changes in pharmacokinetics likely had minimal impact on pharmacodynamic outcomes, as no meaningful correlation was observed between pharmacokinetic and pharmacodynamic parameters. This indicates a lack of a consistent pharmacokinetic–pharmacodynamic relationship in either treatment condition. Based on the integrated pharmacokinetic–pharmacodynamic findings, dose adjustment of metformin does not appear to be warranted when used in combination with OJS.

Typically, drug interaction studies are conducted with 10 to 40 participants, depending on the objective of the study and the intra-individual variability of pharmacokinetic parameters. Previous pharmacokinetic interaction studies involving metformin have included relatively small sample sizes, ranging from about 6 to 20 subjects.[9] The reported coefficient of variation (CV) for metformin's AUC is approximately 13% with a range of 4 to 23%.[21] In our study, the within-subject CV for AUC_{last} was around 15%, and a post hoc power analysis indicated a statistical power of 87.75%. Based on these findings, a sample size of 15 participants in the present study is considered adequate to evaluate pharmacokinetic changes with acceptable precision and reliability.

This study represents the first prospective investigation to evaluate the impact of OJS on pharmacokinetics and glucose-lowering effects when co-administered with metformin. However, several limitations should be acknowledged. First, the study enrolled only healthy volunteers rather than diabetic patients. Differences in physiological and metabolic conditions between healthy individuals and diabetic patients could influence the pharmacokinetic and pharmacodynamic responses. Although one retrospective study reported a glucose-lowering effect of OJS in diabetic patients without renal impairment when combined with hypoglycemic agents, including metformin,[27] the evidence remains limited and observational. Second, the current study focused exclusively on male volunteers, which may pose limitations on the generalizability of our findings to female populations. However, previous studies have demonstrated no significant differences in metformin's pharmacokinetics between sexes, suggesting that our conclusions may also be applicable to females.[28,29] Additionally, this prior study comparing healthy individuals with DM patients without renal impairment found no significant differences in metformin AUC, supporting the relevance of our data to DM patients without renal impairment.[29] Nevertheless, the literature and clinical guidelines recommend dose reduction or cautious use of metformin in diabetic patients with impaired renal function.[30,31] Consequently, the pharmacokinetic and glycemic effects of OJS when co-administered with metformin may differ in patients with renal impairment compared

to those who are healthy or have preserved renal function. These considerations underscore the need for further long-term, prospective clinical studies involving larger and more diverse patient populations, along with comprehensive safety evaluations.

Conclusion

This study evaluated the pharmacokinetic and pharmacodynamic effects of OJS on metformin in healthy male volunteers through an open-label, single-sequence, crossover clinical design. The co-administration of OJS and metformin decreased the plasma concentrations of metformin. However, considering the GMR of C_{max} and AUC_{last}, the degree of decrease was not clinically significant. Additionally, considering the OGTT results, it was determined that these changes in metformin concentration did not affect glucose concentration. Although this study was conducted in healthy participants, further research is warranted to assess potential changes in glucose levels in diabetic patients. Nonetheless, based on the present findings, the impact of co-administration on glycemic control in diabetic patients is expected to be minimal.

Data Sharing Statement

The data can be made available upon request from the corresponding author.

Ethics Statement

This open-label, single-sequence, crossover clinical study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice (Clinical Research Information Service, CRIS [https://cris.nih.go.kr]; registry number: KCT0006799). The protocol and informed consent forms were approved by the Korean Ministry of Food and Drug Safety, the institutional review board (IRB, IRB number: KHUH 2021-05-007) of Kyung Hee University Hospital (KHUH, Seoul, Republic of Korea), and IRB (IRB number: KOMCIRB 2021-06-004) of Kyung Hee University Korean Medical Hospital (KHUKMH, Seoul, Republic of Korea).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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