

Effect of *Helicobacter pylori* eradication on insulin resistance among prediabetic patients: A pilot study and single-blind randomized controlled clinical trial

Ali Kachuei, Masoud Amini, Vahid Sebghatollahi¹, Awat Feizi², Pooria Hamedani, Bijan Iraj

Departments of Endocrinology, ¹Gastroenterology and ²Biostatistics and Epidemiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Type II diabetes mellitus (T2DM) is the prevalent type of diabetes in the world. Prediabetic patients are the most probable group to get diabetes. Several studies have mentioned the role of inflammation in the incidence of diabetes. The origin of inflammation can be infection such as *Helicobacter pylori* (HP) infection. This study was designed to explore the effect of HP eradication on insulin resistance. **Materials and Methods:** This single-blind randomized controlled clinical trial was conducted in 2014-2015. The sample size consisted of 49 individuals who were in prediabetes stage with HP infection. Patients with positive stool antigen were allocated randomly into two groups. The treatment group took medication to eradicate HP infection by the routine method of four-drug eradication. However, placebo capsules and tablets were given to the patients in the placebo group. Then fasting plasma glucose (FPG), fasting plasma insulin (FPI), and quantitative C-reactive protein (CRP) levels were measured and homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of beta-cell function (HOMA-B), Matsuda index, insulinogenic index, and disposition index were calculated. **Results:** Results of this study showed that FPI and HOMA-IR increased significantly (P value of FPI = 0.023 and P value of HOMA-IR = 0.019) after HP eradication in the treatment group. On the other hand, comparison of differences at the baseline and after 6 weeks in FPG (P value = 0.045), FPI (P value = 0.013), and HOMA-B (P value = 0.038) revealed significant differences between the placebo group and treatment group. **Conclusion:** Results showed that HP eradication by a 2-week antibiotic medication did not decrease insulin resistance and even increased FPI and insulin resistance indices. So HP eradication among prediabetic patients is not recommended for the decrease of insulin resistance and postponement of the development of diabetes mellitus.

Key words: *Helicobacter pylori* (HP) infection, insulin resistance, prediabetic

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INTRODUCTION

Type II diabetes mellitus (T2DM) is the prevalent type of diabetes including 90% of the cases in the world. In both developed and developing countries, it is becoming epidemic; however, the burden of this disease seems disproportionate in non-European countries. The number of patients was reported to be 285 million in 2010 and is predicted to reach 438 million in 2030. This

rapidly growing prevalence makes it an important issue in public health. The World Health Organization has reported that the prevalence of T2DM will be 6.8% in Iran in 2025, accounting for approximately 5,215,000 cases. This figure will exceed 6.4 million in 2030.^[1] The expert committee on diagnosis and classification of diabetes mellitus suggested the screening of asymptomatic adults including individuals with body mass index (BMI) more than 25 kg/m² or 23 kg/m² in Asian Americans, physical inactivity, family history of diabetes among first-degree relatives, high-risk race, delivering a baby

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Address for correspondence: Dr. Pooria Hamedani, Department of Endocrinology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: pooria.hamedani@yahoo.com

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weighing heavier than 4.1 kg, blood pressure more than 140/90 mmHg, high-density lipoprotein (HDL) cholesterol level less than 35 mg/dL or triglyceride level more than 250 mg/dL, history of polycystic ovary syndrome, A1C more than 5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) on previous testing, and history of cardiovascular disease (CVD).^[2]

Among risk groups, prediabetics are the most probable group to get diabetes. Prediabetes is a stage with a high level of blood glucose but it is not as high as the level in diabetes. Also, it is called IGT or IFG too.^[3] Prediabetic patients are at risk of microvascular and macrovascular diseases.^[4] The prediabetic stage may be diagnosed by A1C assessment or plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT). So prediabetes is categorized into three groups:

1. IFG with FPG between 100 mg/dL and 125 mg/dL.
2. IGT with 2-h PG between 140 mg/dL and 199 mg/dL.
3. A1C between 5.7% and 6.4%.^[2]

The detection of diabetes pathogens and causes can help to prevent diabetes among prediabetic patients. One of these causes is resistance to insulin, which has a significant effect on the progress of the disease. Insulin resistance and metabolic syndrome can end in obesity, hyperlipidemia, hypertension, vascular endothelial dysfunction, and nonalcoholic fatty liver diseases, all of which increase the risk of diabetes and CVD.^[5-6] Several studies have mentioned the role of inflammation in the incidence of diabetes and insulin resistance. The origin of inflammation can be infections such as *Helicobacter pylori* (HP) infection.^[7] The relation between HP infection and diabetes was mentioned for the first time in 1989.^[8] Chronic HP infection affects the hormonal function of the digestive system and consequently can increase insulin resistance.^[9] On the other hand, immunosuppression in diabetes predisposes diabetic patients to develop HP infection; this could explain the high prevalence of HP infection among diabetics.^[10-11] The association of HP infection with gastric carcinoma was investigated;^[12] so it can be assumed that gastrointestinal disorders among diabetics are due to HP infection.

HP is a Gram-negative, microaerophilic bacterium, which causes stomach infection in more than 50% of the world's population; it is one of the prevalent infections, which causes acute gastritis, peptic ulcer, and stomach cancer.^[13] Studies have shown that this infection not only leads to local inflammation in the digestive system but also ends in systematic inflammation and the incidence of CVD, immune thrombocytopenia, iron deficiency anemia, diabetes mellitus, and insulin resistance.^[10,14-22] On the other hand, HP infection can cause CVD by insulin resistance.^[5-6]

Although several studies have confirmed the relationship between HP infection and insulin resistance, Polyzos *et al.*^[23] mentioned the necessity of much research on this. In a study by Malamug *et al.*,^[24] no significant association was seen between HP infection and insulin resistance among 4,136 healthy persons with different races.

Considering related researches and paradoxical results in some of them and the possible effect of race, apart from the lack of similar study in Iran, this study was designed to explore the effect of HP eradication on insulin resistance factors such as FPG, homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of beta-cell function (HOMA-B), Matsuda, insulinogenic, and disposition indices.

MATERIALS AND METHODS

This single-blind randomized controlled clinical trial was conducted in 2014-2015. The target population was prediabetic patients with HP infection. Initially, 113 patients were chosen by simple random selecting from the referred patients to the Endocrinology and Metabolism Research Center, Isfahan University of Medical Sciences. Five patients were excluded from the study because of diabetes and 29 patients for being in the nonprediabetic stage. Twenty-three cases were prediabetic but the HP test was negative for them due to which they were excluded too. The remaining 56 individuals were entered into the study and randomly allocated to either the treatment group or the placebo group. Seven patients were lost to follow-up and the final sample size was 49 individuals comprising those who were in the prediabetic stage with HP infection. The flowchart of study is shown in Figure 1.

Approval was granted by Isfahan University of Medical Sciences' ethic committee for the study protocol (project number: 394346). All the participants filled the informed consent form after an explanatory session.

Inclusion criteria were prediabetic patients with HP infection and also without the presence of diabetes, rheumatoid arthritis, chronic kidney disease, alcohol consumption, cancer, systematic or localized infection, no history of consumption of H2 blocker, proton pump inhibitor, bismuth and any antibiotic within the last 4 weeks, history of nonsteroidal anti-inflammatory drug (NASID), glucocorticoid and contraceptive drug consumption and history of any antidiabetes drug consumption, history of gastrointestinal surgery-like bypass, history of peptic ulcer (stomach and duodenal ulcers), history of HP treatment, pregnancy, and age less than 16 years and more than 70 years. Exclusion criteria were unwillingness to participate, loss to follow-up because of not participating, pregnancy,

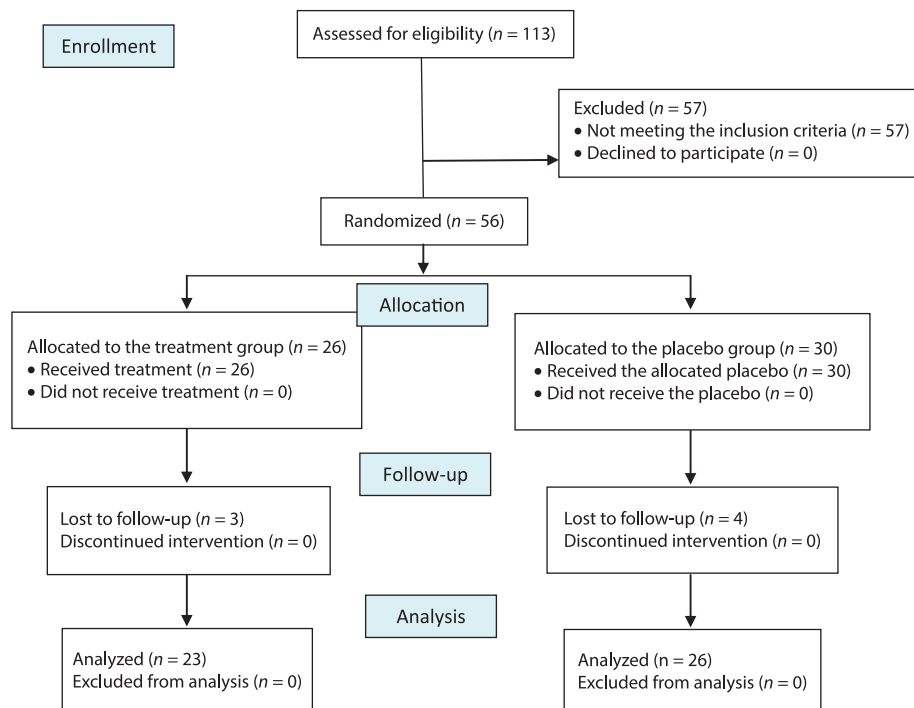


Figure 1: CONSORT flowchart for the two treatments of the study

the start of diabetes, and change in the clinical status interfering with treatment.

The prediabetic status of patients was confirmed by either IGT in 75-g OGTT or IFG or both. Then HP stool antigen test was performed for patients and according to the results, they were categorized into two groups: Positive stool antigen and negative stool antigen. OGTT test was performed for all the patients and blood samples were taken in fasting time (after 8 h of fasting) and 30 min, 60 min, and 120 min after consumption of 75-g oral glucose.^[25] Then FPG, fasting plasma insulin (FPI), and quantitative C-reactive protein (CRP) were measured in fasting samples and the levels of plasma glucose and plasma insulin were measured in other samples.

Patients with positive stool antigen were allocated randomly into two groups by random allocation software. The treatment group took medication including omeprazole capsules 20 mg, amoxicillin capsules 1 g, clarithromycin capsules 500 mg, and bismuth subcitrate 240 mg twice daily for 14 days to eradicate HP infection.^[26] The possible side effects of all the drugs were described to all patients and an emergency telephone number was available for them. Compliance with tablet consumption was checked by tablet counting. After a 2-week medication, patients were followed up for 4 weeks and then the stool antigen test was repeated again in order to evaluate the effectiveness of treatment. Also, OGTT test was repeated and blood samples were taken and FPG, FPI, and quantitative CRP levels were measured.

In the placebo group, there was no intervention. However, placebo capsules and tablets, identical to the study drugs with a similar schedule, were given to the patients in the placebo group. Concurrently, OGTT test was performed and blood samples were taken at the baseline and after 6 weeks. Then FPG, FPI, and quantitative CRP levels were measured.

Waist circumference (centimeters) was measured by locating the uppermost border of the hip bones on right-hand side and aligning the bottom edge of the measuring tape with the top of the hip bones. In both the groups, HOMA-IR, HOMA-B, Matsuda index, insulinogenic index, and disposition index were calculated as follows:

$$\text{HOMA-IR} = \text{FPI (mU/L)} \times \text{FPG (mmol/L)} / 22.5^{[24]}$$

$$\text{HOMA-B} = (\text{FPI (mU/L)} \times 20) / (\text{FPG (mmol/L)} - 3.5)^{[24]}$$

$$\text{Matsuda index} = 10000 / \sqrt{\text{FPG (mg/dL)} \times \text{FPI (mU/L)} \times \text{PG}_{\text{mean}} \times \text{PI}_{\text{mean}}}$$

Where PG_{mean} and PI_{mean} are mean plasma glucose concentration during OGTT (mg/dL) from 0 min to 120 min and mean plasma insulin concentration during OGTT (mIU/L) from 0 min to 120 min, respectively.^[27]

$$\text{Insulinogenic index} = \frac{(\text{PI}_{30 \text{ min}} - \text{PI}_{0 \text{ min}}) / (\text{PG}_{30 \text{ min}} - \text{PG}_{0 \text{ min}})}{\left(\frac{\text{mU/L}}{\text{mmol/L}}\right)} \text{ where } \text{PI}_0 \text{ and } \text{PI}_{30 \text{ min}} \text{ are plasma insulin at 0 min}$$

and 30 min, respectively, and $PG_{30\text{min}}$ and $PG_{0\text{min}}$ are plasma glucose at 0 min and 30 min, respectively.^[28]

Disposition index = Matsuda index \times Insulinogenic index^[27]

Serum glucose concentration and quantitative CRP was measured by BT3000 and the usual trademark kits (Pars kit). Also, the serum insulin level was measured by automated chemiluminescence immunoassay method (Advia Centaur CP, Siemens Healthcare Diagnostic Inc, USA).

Statistical methods

In this study, descriptive statistics including mean \pm standard deviation (SD), median, and frequency and statistical tests such as chi-square and Fisher's exact test for testing the independency of categorical variables, parametric independent, and dependent *t*-test for comparing the means, nonparametric Mann–Whitney test, and Wilcoxon test for comparing the medians were used. All analyses were done with IBM SPSS Statistic (IBM Corp. Released 2011, Version 20.0, Armonk, New York). The significant level was considered 0.05.

RESULTS

The means of age in the placebo group and treatment group were 52.39 ± 7.44 years and 52.27 ± 5.14 years, respectively. Nearly 65% of the placebo group and 54% of the treatment group were females. In the placebo group, 82.6% and in the treatment group 88.5% had family history of diabetes mellitus (FHDM). HP eradication rate was 88.5% in the treatment group. No significant difference was seen between the two groups in the baseline characteristics except for systolic blood pressure (*P* value < 0.05); it was higher in the treatment group than in the placebo group. The other demographic and laboratory findings are shown in Table 1.

Some significant differences were seen at the baseline and after 6 weeks in the treatment group including the increase of FPI (*P* value = 0.023), HOMA-IR (*P* value = 0.019), and systolic blood pressure (SBP) (*P* value = 0.001). There was no significant change in the placebo group [Table 2].

The comparison of the mean of variables between the baseline and after 6 weeks showed a significant difference between the two groups in FPG (*P* value = 0.045), FPI (*P* value = 0.013), SBP (*P* value = 0.003), and HOMA-B (*P* value = 0.038). The difference in the means of FPI and HOMA-B was positive in the treatment group; however, it was negative in the placebo group. On the other hand, negative difference in the mean of SBP was seen in the treatment group [Table 3].

DISCUSSION

The aim of this research was to study the effect of HP eradication on insulin resistance indices among prediabetic patients. There are several studies, which confirmed the relationship between HP infection and insulin resistance.^[23-24,29-35] Among them, some researches specifically studied the effect of HP eradication on insulin resistance. In a study by Dogan *et al.*,^[30] 370 patients with HP infection were chosen and treated for HP. Then they were followed up for 6 months after eradication. The results showed a significant decrease in FPG, FPI, HbA1c, and HOMA-IR after eradication as compared to before eradication. In another prospective study by Gen *et al.*,^[29] 159 patients with (*n* = 88) and without (*n* = 71) HP infection were studied. Patients with HP infection were put on a 14-day HP eradication regimen. In the HP infection group, HOMA-IR, total cholesterol (TC), triglyceride (TG), LDL cholesterol, and CRP were higher and HDL cholesterol was lower. Also, after eradication therapy during 6 weeks, HOMA-IR, TC, TG, LDL, and CRP decreased too.

Table 1: Demographic and laboratory characteristics of patients

Variable	Placebo (<i>n</i> = 23)	Treatment (<i>n</i> = 26)	<i>P</i> value	Power
Age (years)	52.39 \pm 7.44	52.27 \pm 5.14	0.948 ¹	0.530
Sex			0.419 ³	0.321
Male	8 (34.8%)	12 (46.2%)		
Female	15 (65.2%)	14 (53.8%)		
FPG (mg/dL)	108.69 \pm 7.21	109.96 \pm 6.76	0.529 ¹	0.530
FPI (mU/L)	10.98 \pm 6.67	9.26 \pm 3.89	0.268 ¹	0.530
CRP (mg/dL)	1.08 \pm 0.31	1.09 \pm 0.21	0.941 ¹	0.530
Waist (cm)	97.06 \pm 8.94	97.27 \pm 9.02	0.937 ¹	0.530
SBP (mmHg)	110	125	0.003 ²	0.889
DBP (mmHg)	80	77.5	0.688 ²	0.514
HTN			1 ⁴	0.56
Negative	20 (87%)	21 (81%)		
Positive	3 (13%)	5 (19%)		
FHDM			0.692 ⁴	0.56
Negative	4 (17.4%)	3 (11.5%)		
Positive	19 (82.6%)	23 (88.5%)		
Smoking			1 ⁴	0.56
Nonsmoker	22 (95.7%)	24 (92.3%)		
Smoker	1 (4.3%)	2 (7.7%)		
Dyspepsia			0.363 ³	0.321
Negative	9 (39.1%)	7 (26.9%)		
Positive	14 (60.9%)	19 (73.1%)		
HOMA-IR	2.94 \pm 1.84	2.52 \pm 1.11	0.329 ¹	0.530
HOMA-B	88.48 \pm 52.04	72.02 \pm 31.04	0.179 ¹	0.530
Matsuda index	4.40 \pm 2.22	4.74 \pm 2.08	0.586 ¹	0.530
Insulinogenic index	12.51	11.83	0.875 ²	0.514
Disposition index	51.46	50.44	0.521 ²	0.514

¹Independent *t*-test (mean \pm SD); ²Mann–Whitney *U* test (median); ³Chi-square test [frequency (%)]; ⁴Fisher's exact test [frequency (%)]

Table 2: Results of laboratory variables at the baseline and after 6 weeks in the placebo group and treatment group

Variable	Group	Baseline	After 6 weeks	P value	Power
FPG	Placebo	108.69±7.21	110.04±23.83	0.787*	0.539
	Treatment	109.96±6.76	112.23±8.97	0.226*	0.539
FPI	Placebo	10.98±6.67	9.59 ± 5.42	0.194*	0.539
	Treatment	9.26±3.89	11.33±5.68	0.023*	0.806
CRP	Placebo	1.08±0.31	1.07±0.18	0.948*	0.539
	Treatment	1.08±0.21	1.10±0.21	0.711*	0.539
Waist	Placebo	97.06±8.93	97.06±10.48	1*	0.539
	Treatment	97.27±9.02	96.63±9.54	0.221*	0.539
SBP	Placebo	110	110	0.447**	0.519
	Treatment	125	112.5	0.001**	0.966
DBP	Placebo	80	80	0.327**	0.519
	Treatment	77.5	79	0.699**	0.519
HOMA-IR	Placebo	2.94±1.84	2.71±2	0.589*	0.539
	Treatment	2.52±1.11	3.16±1.68	0.019*	0.843
HOMA-B	Placebo	88.48±52.05	79.08±43.52	0.227*	0.539
	Treatment	72.02±31.04	84.01±39.01	0.082*	0.539
Matsuda index	Placebo	4.40±2.22	4.89±2.37	0.233*	0.539
	Treatment	4.74±2.08	4.43±2.36	0.346*	0.539
Insulinogenic index	Placebo	12.51	11.94	0.935**	0.519
	Treatment	11.83	11.69	0.485**	0.519
Disposition index	Placebo	51.46	52.39	0.485**	0.519
	Treatment	50.44	40.71	0.200**	0.519

*Paired t-test (mean ± SD); **Wilcoxon test (median)

Table 3: Difference mean of measurements at 6 weeks from the baseline in the placebo group and treatment group

Variable	Placebo (n = 23)	Treatment (n = 26)	P value	Power
FPG (mg/dL)	-3	3.5	0.045**	0.514
FPI (mU/L)	-1.39±5	2.07±4.34	0.013*	0.816
CRP (mg/dL)	-0.003±0.28	0.02±0.27	0.764*	0.53
Waist (cm)	0±4.15	-0.63±2.58	0.519*	0.53
SBP (mmHg)	1.61±9.19	-7.80±11.11	0.003*	0.937
DBP (mmHg)	-1.74±8.05	-0.96±8.14	0.739*	0.53
HOMA-IR	-0.23±2.05	0.64±1.30	0.077*	0.53
HOMA-B	-9.40±36.25	11.99±33.78	0.038*	0.676
Matsuda index	0.49±1.92	-0.31±1.64	0.123*	0.53
Insulinogenic index	-0.39	-1.73	0.934**	0.514
Disposition index	4.98	-15.10	0.207**	0.514

*Independent t-test (mean ± SD); **Mann-Whitney U test (median); FPG = Fasting plasma glucose; FPI = Fasting plasma insulin; CRP = C-reactive protein; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HOMA-IR = Homeostatic model assessment of insulin resistance; HOMA-B = Homeostatic model assessment of beta-cell function

In the current study, FPI and HOMA-IR levels (as insulin resistance indices) increased in the treatment group after 2-week medication for HP eradication and 4-week follow-up (overall 6 weeks). Apart from unchanged Matsuda index (as an insulin sensitivity index) and insulinogenic and disposition indices (as insulin secretion indices), this increase showed a rising insulin resistance, which can be attributed to the side effect of antibiotics or HP eradication.

Also, significant difference of FPI and HOMA-B (as an insulin secretion index) between the treatment group and placebo group confirmed increasing insulin resistance of the treatment group. In fact, in contrast to other studies,^[23-24,29-35] HP eradication with antibiotics did not improve insulin resistance but increased it.

In some studies, the effect of HP eradication was explored among healthy individuals^[29,30,36] and the effectiveness of medication on insulin resistance was concluded. However, in this study prediabetic patients were chosen. Similar to diabetic patients, they experienced insulin resistance due to several factors (multifactorial nature) including genetic factors. So there are several uncontrolled factors except HP, as an origin of systematic inflammation, and consequently insulin resistance indices did not decrease significantly. On the contrary, healthy individuals in previous studies were not influenced by an important factor such as diabetes genetics.

Finally, not a very strong significant difference of FPG between the two groups (P value = 0.045) could have been due to the variability of FPG test. This hypothesis can be investigated by A1c test with less variability.

There were some limitations in our study. The effect of antibiotics in the 2-week medication on normal flora of gastrointestinal tract was not known. Also, the positive and negative effects of medication on insulin secretion according to incretin hormones were not studied. The small sample size was another limitation of this study. This limitation makes the interpretation of the nonsignificant test invalid.

On the other hand, existence of the control group was one of the strong points of this study. A short interval (6 weeks) between the two measurements helped to control confounders such as lifestyle change.

Also, considering most of the insulin resistance indices such as insulin sensitivity and insulin secretion indices led to better analysis.

CONCLUSION

In this single-blind randomized control trial among prediabetic patients, the results showed that HP eradication by the 2-week antibiotic medication did not decrease insulin resistance and even increased FPI and insulin resistance indices. So HP eradication among prediabetic patients is not recommended for the decrease of insulin resistance and postponement of the development of diabetes mellitus.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

PH contributed in the conception and design of the work, conduct of the study, data acquisition, analysis and interpretation of data, drafting, revision of the draft, approval of the final version of the manuscript, and agreed regarding all aspects of the work.

AK contributed in the conception and design of the work, revision of the draft, approval of the final version of the manuscript, and agreed regarding all aspects of the work.

VS contributed in the conception and design of the work and agreed with all aspects of the work.

MA contributed in interpretation of data, revision of the draft, approval of the final version of the manuscript, and agreed regarding all aspects of the work.

BI contributed in the analysis and interpretation of data and agreed regarding all aspects of the work.

AF contributed in the conception and design of the work, analysis of data, drafting, and agreed regarding all aspects of the work.

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