Reduction of HbA1c levels by fucoxanthin-enriched akamoku oil possibly involves the thrifty allele of uncoupling protein 1 (UCP1): a randomised controlled trial in normal-weight and obese Japanese adults

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Abstract

Lifestyle-related problems are becoming a major health threat in East Asian countries. Therefore, finding an efficacious nutraceutical for this population is important. One candidate is fucoxanthin (Fx), a carotenoid abundantly found in edible brown seaweed that has been associated with a number of valuable health-promoting benefits. Unfortunately, clinical studies of Fx are limited. In the present study, we aimed to evaluate the effects of Fx on obesity-related parameters in Japanese subjects harbouring an SNP associated with lifestyle-related problems. In all, sixty normal-weight and obese Japanese adults with BMI over 22 kg/m2 were single-blinded and randomly assigned to three Fx-dose cohorts and administered Fx-enriched akamoku oil containing Fx at 0, 1 or 2 mg/d for 8 weeks (n 20 per group). Parameters relating to obesity and serum Fx metabolites were measured before and after intervention, but no significant differences were observed between and within the groups. Despite no changes in visceral fat areas and resting energy expenditures after intervention, we observed a significant decline in HbA1c levels in the 2 mg/d Fx group compared with that in the 0 mg/d group (P<0·05), which was correlated with an increase in serum fucoxanthinol (Fx metabolite) levels. In addition, HbA1c levels declined more significantly in subjects with G/G alleles of the uncoupling protein 1 (UCP1) gene than in those with the A/A and A/G alleles (P<0·05). We conclude that although Fx supplementation does not affect visceral fat areas, it may reduce HbA1c levels in those harbouring the thrifty allele of UCP1-3826A/G.

Key words: UCP1-3826A/G polymorphism: Fucoxanthin: HbA1c: Thrifty gene: Japanese: Diabetes: Glucose metabolism

Fucoxanthin (Fx) is a marine carotenoid widely found in edible brown algae such as wakame (Undaria pinnatifida), kombu (Laminaria japonica) and akamoku (Sargassum horneri). It constitutes more than 10% of naturally produced carotenoids(1), providing an abundant reserve of unutilised resources in the ocean. Out of the fifteen species of brown algae that have been studied, akamoku contains the highest content of Fx(2), making it an excellent source for the raw material in our study. Fx has demonstrated beneficial effects against obesity(3,4), diabetes(5) and cancer(6). However, despite proven effects in animal studies, only a few studies on kinetics(7,8) and obesity(9) have been conducted in human subjects. There is one report

Abbreviations: β2AR, β2-adrenoreceptor gene; β3AR, β3-adrenoreceptor gene; Fx, fucoxanthin; FxOH, fucoxanthinol; REE, resting energy expenditure; UCP1, uncoupling protein 1.

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demonstrating that the supplement Xanthigen®, a product that contains Fx and pomegranate seed oil, induces weight loss and body fat reduction, and increases resting energy expenditure (REE) in obese women(9). However, that study was based on the Caucasian population in Russia; thus, the supplement’s effects on East Asian populations remain unclear. Furthermore, no reports have evaluated Fx absorption, serum metabolite (fucoxanthinol; FxOH) levels and functionality. Our study will help expand the knowledge base in these areas.

Although inactive, food-satiated lifestyles dramatically increase the incidence of obesity and related metabolic disorders, the interaction between environmental and genetic factors greatly influences health and susceptibility to disease(10). Therefore, a tailored nutritional approach based on the individual and the population’s genetic background, as characterised by SNP analysis, is required to consider the effectiveness of nutraceuticals.

Uncoupling protein 1 (UCP1) is a thermogenic protein that dissipates glucose and lipid as heat. We investigated how Fx affects glucose metabolism with an SNP of the UCP1 gene (−3826A/G)(11), the thrifty G/G genotype, which is associated with the development of obesity and insulin resistance(12) In addition, we analysed polymorphisms of other thrifty genes, β2-adrenoreceptor (β2-AR) and β3-adrenoreceptor (β3-AR), which also decrease energy expenditure(13,14).

Through our research, we aimed to elucidate the role of Fx in the development of metabolic disorders such as obesity and diabetes, and study the effect of genetic variation in the Japanese adult population on its function.

Materials and methods

Materials

Fx capsules were purchased from Kaneka Corporation. Fx-enriched akamoku oil (containing 1 % Fx) derived from akamoku extract, and medium-chain TAG oil containing lecithin and vitamin E were used to manufacture the Fx soft-gel capsules. Each capsule contained Fx-enriched akamoku oil at the doses of 0 mg (Fx 0 mg, hereafter), 110 mg (Fx 1 mg, hereafter), or 220 mg (Fx 2 mg, hereafter) (Table 1). All capsules appeared identical.

Subjects

A total of sixty normal-weight and obese Japanese adult men and women with BMI ≥ 22 kg/m² were included in the study in Rumoi, Hokkaido, Japan. The group consisted of twenty men and forty women who ranged in age from 30 to 77 years. Written informed consent was obtained from all subjects. Pregnant and lactating women and those unable to give consent were excluded from the study.

Study design

This study was an 8-week, single-centre, randomised, single-blinded, controlled clinical trial conducted from November 2013 to March 2014.

Following simple randomisation procedures (computerised random numbers)(15), our subjects were single-blinded and randomly assigned to three treatment groups (allocation ratio, 1:1:1): Fx 0 mg/d (placebo control), Fx 1 mg/d or Fx 2 mg/d. The subjects were told to take one capsule per d after dinner for 8 weeks and maintain their normal diet and physical activity.

This study was conducted according to the guidelines of the Declaration of Helsinki, and our study protocol and all procedures involving human subjects were approved by the local research ethics committee in Rumoi Cohortopia (#13-01) and registered with the University Hospital Medical Information Network Clinical Trials Registry (trial number UMIN000020119; http://www.umin.ac.jp/). This report follows the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist (http://www.consort-statement.org/).

Visceral fat analyses

Before and after the 8-week supplementation period, abdominal visceral fat areas (primary outcome of this study) were measured in a supine position via computed tomography scans using an Aquilion 64 (Toshiba Medical Systems Corporation) at the Rumoi City Hospital (Hokkaido, Japan).

Resting energy expenditure measurements

Before and after the 8-week supplementation period, REE was determined with a MedGem metabolic analyser device (HealthTech, Inc.), a portable indirect calorimeter that we used for 10 min (as recommended by the manufacturer) to measure O₂ consumption(16).

Blood biochemical markers

Before and after the 8-week supplementation period, blood samples were drawn after 12 h of fasting to assess secondary outcomes. The following levels were measured: blood glucose, HbA1c, serum insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol, TAG, aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase. Glycated albumin levels were measured before and after intervention only in UCP1 G/G carriers who were administered Fx 2 mg/d. While blood glucose is the amount of glucose present in blood at any given time, glycated albumin and HbA1c (glycated Hb) reflect the cumulative glycaemic history (average glycaemic levels over the previous 2 weeks and 3–4 months, respectively)(17). Serum insulin is an indicator of insulin
secretion in a sample population. Total cholesterol, HDL-cholesterol, LDL-cholesterol and TAG reflect lipid metabolism, whereas HDL- and LDL-cholesterol, and TAG levels are used for diagnosing dyslipidemia. Aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase are enzymes related to liver function and are used to evaluate the hepatic toxicity of Fx.

**Serum fucoxanthinol analysis**

To quantify serum FxOH levels (a major metabolite of Fx), serum epoxysxanthophyll fractions that included FxOH were extracted and analysed by a liquid chromatography–tandem MS (LC-MS/MS) system as previously developed by the authors and described below. We used Fx as the internal standard because Fx is structurally similar to FxOH(18), the two have comparable solvent properties, and a preliminary experiment revealed that Fx is not detectable in the serum after its intake.

The extraction was performed according to the method developed by Asai et al.(8), with a slight modification. In brief, 1 ml of serum, 0.2 ml of saline and 2 ml of methanol that included 5 ng of Fx as an internal standard were added to a glass tube and vortexed. The residue was dissolved in n-hexane–diethyl ether (9:1, v/v) and applied to a Bond Elut ALN (100 mg, 1 ml) solid–phase extraction cartridge (Agilent Technologies) pretreated with 1 ml n-hexane. Epoxysxanthophylls eluted with 1 ml diethyl ether–ethanol (4:1, v/v) were dried and re-suspended in 250 µl of methanol–acetonitrile (70:30, v/v), and then 50 µl of the sample was subjected to LC-MS/MS analysis. Each serum sample was independently extracted and analysed in triplicate.

Our liquid chromatography system was composed of an Agilent 1100 series degasser, binary pump, auto-sampler, column oven (Agilent Technologies) and Inertsil®-ODS column (4.6 mm inner diameter × 150 mm, 3 µm, GL Sciences Inc.). The HPLC mobile phases were solvent A (methanol–acetonitrile, 70:30, v/v) and solvent B (dichloromethane). Elution after sample injection was performed as follows: 0–5 min, 0 % B; 5–25 min, 0–100 % B; 25–50 min, 100 % B; 50–60 min, 0 % B. The flow rate was maintained at 1 ml/min at 35 °C. FxOH was detected at 2.3 min. The amount of FxOH in the serum was calculated from the peak area counts of the spiked internal standard.

**Analysis of UCP1 gene polymorphism**

For analysis of SNP, genomic DNA was isolated from whole-blood samples of each subject using a DNA solution kit (Qiagen). Polymorphisms of UCP1-3826A/G (rs1800592), β2-AR 16 Arg/Gly (rs1042713) and β3-AR 64 Trp/Arg (rs4994) were determined using a Toyobo Gene analysis system (Fukui) as described by Yamada et al.(19).

**Statistics**

The sample size (n 20 per group) was calculated from a previous study reporting a 10 % reduction of body weight for obese subjects(8). Twenty participants were estimated to be sufficient to set the power of the trial at 80 % with a significance level of 5 % for detecting significant body-weight reduction. That number allowed for a 20 % dropout rate from each group.

Results are expressed as means and standard errors. Data were verified for normality by the Shapiro–Wilk test. When necessary, they were log-transformed for normal distribution before further statistical analysis for homogeneity of variance. Parametric comparisons were performed using t tests, one-way ANOVA and the Tukey–Kramer test for multiple comparisons. If normal distribution and equality of variance tests were not performed, Welch’s test was used, and, if necessary, a non-parametric Steel–Dwass test. For the genotype frequency of UCP1-3826A/G, Fisher’s exact test was performed. For G/G carriers administered Fx 2 mg/d, albumin levels were measured before and after intervention, then analysed by paired t test. In all cases, P values < 0.05 were considered statistically significant. All analyses were performed using JMP® 10.0.0 and 10.0.2 (SAS Institute Inc.) or R version 3.2.0.

**Results**

**Characteristics of subjects**

This study was a single-blinded, randomised intervention trial. A total of sixty healthy participants provided informed consent regarding the aims of this clinical trial. Allocation, follow-up and analysis are summarised in Fig. 1.

At baseline, the subjects were evenly distributed in terms of age, sex, BMI, visceral fat area, REE and all blood biochemical markers (Table 2). Overall, the mean age was 55 (SE 2) years (range 30–77 years) and the mean BMI was 26.4 (SE 0.4) kg/m² (range 22.4–34.9 kg/m²). Because the Japan Society for the Study of Obesity defines 18·5 ≤ BMI < 25 kg/m² as normal weight and BMI ≥ 25 kg/m² as obese(20), our population included twenty-six normal-weight and thirty-three obese subjects. One man in the Fx 1 mg/d group dropped out for private reasons. The follow-up rate was 98·3 %, and no adverse events were reported. After intervention, no significant differences for any of the parameters were observed among the three groups (Table 2). Furthermore, comparisons within groups (baseline vs. after intervention) also revealed no significant differences (Table 2).

**Fucoxanthin did not change obesity-related outcomes**

Fx intervention did not change visceral fat areas (change in the Fx 0, 1 and 2 mg/d groups were −6·6 (SE 3·6), −8·6 (SE 5·4) and −5·7 (SE 3·4) cm², respectively). Other obesity-related outcomes such as body weight, BMI and REE also remained unchanged in the Fx groups.

**Fucoxanthin reduced HbA1c and increased serum fucoxanthin metabolite levels**

Detailed analysis of biochemical parameters revealed a significant reduction in HbA1c in the Fx 2 mg/d group (−0·14 (SE 0·0) %) compared with that of the 0 mg/d group (0·06 (SE 0·05) %, P < 0·05; Table 3). This was associated with an apparent increase in serum FxOH (P < 0·0001), a metabolite...
of Fx (Table 3). Indeed, significant increases in serum FxOH levels detected between the 1 mg/d and 0 mg/d groups ($P < 0.0001$), and between the 2 mg/d and 0 mg/d groups ($P < 0.0001$) indicated a dose-dependent effect (Table 3), with mean FxOH levels of 2.7 and 2.1 and 0.4 nm, for the 2, 1 and 0 mg/d groups, respectively.

Possible interaction between fucoxanthin supplementation and UCP1-3826A/G polymorphism may influence reduction of HbA1c

As shown in Fig. 2(A), 8 weeks of supplementation with 2 mg/d of Fx significantly reduced HbA1c levels in subjects with the UCP1-3826A/G polymorphism. The reduction in HbA1c levels for the G/G genotype (−0.54 (SE 0.45) %) was significantly greater than that of the A/A (0.05 (SE 0.17) %, $P < 0.05$) and A/G (−0.02 (SE 0.18) %, $P < 0.01$) genotypes. We noted that the sample number for each UCP1-3826A/G genotype was not significantly different among Fx groups ($P = 0.63$, Fisher’s exact test), and that HbA1c levels did not decline in the Fx 0 or 1 mg/d groups (Fig. 2(A)). Additionally, serum FxOH levels were not affected by the UCP1 genotype (Supplementary Fig. S1). Parallel plot analysis confirmed that Fx intervention reduced HbA1c and glycated albumin levels in all Fx 2 mg/d participants who carried the UCP1 G/G allele. $P$ values from the paired t test for changes in HbA1c and glycated albumin (before intervention $v.$ after intervention) were 0.055 and 0.067, respectively (Fig. 2(B)). We could not analyse the involvement of other well-known thrifty genes, such as β3AR 64 Trp/Arg and β2AR Arg/Gly, with Fx-induced reduction of HbA1c because of the lack of carriers for each genotype (Fig. 3).

Baseline parameters were unbiased according to UCP1 genotype

Table 4 shows the baseline characteristics of each UCP1 genotype group. At baseline, the participants of each genotype were evenly distributed in terms of age, sex, BMI, visceral fat area, REE and all blood biochemical markers.

Safety

In the present study, Fx capsules were well tolerated by all participants who completed the 8-week trial. No subjective or
Table 2. Obesity-related parameters for Japanese adults in the fucoxanthin (Fx) intervention groups (0 or 1 or 2 mg/d) at baseline and after intervention*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fx 0 mg</td>
<td>Fx 1 mg</td>
<td>Fx 2 mg</td>
</tr>
<tr>
<td>Subjects</td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>Number</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Male %</td>
<td>20</td>
<td>32</td>
<td>45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.0</td>
<td>57.5</td>
<td>55.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.6</td>
<td>158.2</td>
<td>159.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.8</td>
<td>67.0</td>
<td>70.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2</td>
<td>26.6</td>
<td>27.2</td>
</tr>
<tr>
<td>Visceral fat area (cm²)</td>
<td>91.6</td>
<td>119.4</td>
<td>113.5</td>
</tr>
<tr>
<td>Resting energy expenditure (kcal/d)†</td>
<td>1342</td>
<td>1326</td>
<td>1476</td>
</tr>
<tr>
<td>Blood biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)†</td>
<td>109</td>
<td>107</td>
<td>111</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.4</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>8.2</td>
<td>8.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)†</td>
<td>207</td>
<td>210</td>
<td>205</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)†</td>
<td>59</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)†</td>
<td>121</td>
<td>118</td>
<td>122</td>
</tr>
<tr>
<td>TAG (mg/dl)†</td>
<td>129</td>
<td>177</td>
<td>132</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU)</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU)</td>
<td>21</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase (IU)</td>
<td>47</td>
<td>33</td>
<td>44</td>
</tr>
</tbody>
</table>

* Subjects were randomly assigned to three groups. Comparisons of parameters among the three groups (baseline and after) and within a group (baseline v. after) were performed by t test, one-way ANOVA, Welch’s test and a non-parametric Steel-Dwass test. No significant differences were observed between and within the three groups.
† To convert kcal to kJ, multiply by 4.184; to convert glucose from mg/dl to mmol/l, multiply by 0.0555; to convert cholesterol from mg/dl to mmol/l, multiply by 0.0259; to convert TAG from mg/dl to mmol/l, multiply by 0.0113.
Table 3. Changes in HbA1c levels and serum fucoxanthinol (FxOH) levels in the fucoxanthin (Fx) intervention groups (0 or 1 or 2 mg/d) after the 8-week intervention

<table>
<thead>
<tr>
<th></th>
<th>Fx 0 mg</th>
<th>Fx 1 mg</th>
<th>Fx 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SE</td>
<td>Mean SE</td>
<td>Mean SE</td>
</tr>
<tr>
<td>∆HbA1c (%)</td>
<td>0.06 0.05</td>
<td>0.01 0.05</td>
<td>-0.14* 0.05</td>
</tr>
<tr>
<td>Serum FxOH levels (after 8 weeks) (μu)</td>
<td>0.4 0.0</td>
<td>2.1** 0.2</td>
<td>2.7** 0.4</td>
</tr>
</tbody>
</table>

Mean value was significantly different from that of the 0 mg/d group: *P < 0.05, **P < 0.0001.
† ∆HbA1c represents the change in HbA1c levels before and after an 8-week intervention of Fx. P values for comparison of parameters among the three groups were calculated by one-way ANOVA, the Tukey–Kramer test for multiple comparisons and a non-parametric Steel–Dwass test.

Discussion

Our present study showed that intake of Fx-enriched akamoku oil significantly increased serum FxOH levels in a fashion of Fx dose-dependency. The increase was associated with HbA1c reduction, remarkably in carriers with the G/G allele of the UCP1 gene. These results suggest that Fx intake affects HbA1c reduction in UCP1 polymorphism. Further studies are needed to elucidate a mechanistic link between Fx intake and glucose metabolism in G/G allele carriers.

Genetic variations generate innate characteristics in individuals and the population, as shown by genome-wide association studies. Because of the great diversity and complexity of genetic backgrounds, tailoring healthcare through the use of rational genotyping such as SNP analysis is rising in importance. For instance, the thrifty UCP1 G/G genotype is one of the most well-characterised genes associated with the development of obesity and insulin resistance. It is conceivable that carriers of the G/G allele, comprising over 20% of the East Asian population, could be at high risk for obesity-related disorders. It is also possible that carriers of the G/G allele may respond to treatment differently from the general population. For that reason, we aimed to elucidate the biofunctional effects of Fx on metabolic disorders in the Japanese population.

In a previous study, 8 weeks of supplementation with Xanthigen® (containing Fx and pomegranate seed oil) decreased the body weight of Russian women. However, those results were not reproduced in our study. Indeed, we detected no changes in obesity-related outcomes, including visceral fat area, which could be explained by the many differences between the two study populations (e.g. race, sex, age, body weight and BMI). Further, the reduced body weight in Russian women could have been related to the combined effects of Fx and pomegranate seed oil.

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Orally administered Fx is hydrolysed to FxOH in the intestinal tract, after which it is absorbed and detected in the blood and organs. We noted a dose-dependent increase in serum FxOH that confirmed oral absorption of Fx. Combined with the reduction of HbA1c for the 2 mg/d group (but not the 0 mg/d group), our results strongly suggest that Fx possesses biofunctionality.

Furthermore, we determined that HbA1c reduction was closely linked to the G/G allele of the UCP1 gene. Participants in the 2 mg/d group who carried the UCP1-3826A/G gene polymorphism exhibited a more appreciable reduction in HbA1c levels. HbA1c, glycated Hb that reflects average blood glucose levels, is considered the standard for assessing glucose metabolism over the long term. Additionally, serum levels of glycated albumin (a product of objective adverse effects, including hepatic dysfunction and alterations in lipid metabolism, were reported.
non-enzymic glycation that is also used as a glycaemic indicator) apparently decreased in all subjects in the 2 mg/d group with the G/G genotype. Although an accurate HbA1c measurement is limited by various conditions, including erythrocyte lifespan, normal ageing and other factors(26), the decline in both HbA1c and glycated albumin levels suggests that Fx may aid in glucose metabolism. Taken together, our findings indicate a novel role for Fx: UCP1 genotype-dependent reduction of HbA1c levels in humans, although the mechanism by which Fx exerts this effect remains unclear.

There are other reports supporting a relationship between Fx and UCP1 gene products: UCP1 mRNA expression levels in human intraperitoneal adipose tissue are lower in UCP1 G/G genotype carriers than in the other two genotypes(27), and Fx...
induces UCP1 mRNA and protein expression in murine adipocytes\(^3\). To expand upon our findings on the relationship between Fx and the UCP1 genotype, further studies with more participants are needed. In addition, various formulations of Fx or FxOH might be investigated in addition to Fx oil, such as processed algal materials, food matrix-destruction, mixing with lysoglyceroglycolipids\(^{28}\), and/or addition of egg yolk to FxOH\(^{29}\).

Our data indicate that Fx-induced reduction of HbA1c levels is closely linked to the G/G allele of the UCP1 gene. Fx’s dependence on UCP1 gene polymorphism sheds light on a possible tailored application for this unique carotenoid. Indeed, tailoring a nutraceutical like Fx would be a rational and efficient treatment strategy for genetically high-risk populations.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/jns.2017.1

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N. M. designed the research, analysed and interpreted the data, and wrote the manuscript. M. H. and K. M. formulated the study conception and revised the manuscript. H. S. interpreted and wrote the manuscript. M. H. and K. M. formulated the strategy for the Industrial Seaweed Utilisation Supporting Regional Seeds and Local Features of Sanriku Coast) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and the Japan Society for the Promotion of Science Grants-in-Aid (JSPS KAKENHI grant number JP16K21251).

N. M. designed the research, analysed and interpreted the data, and wrote the manuscript. M. H. and K. M. formulated the study conception and revised the manuscript. H. S. interpreted the data and wrote the manuscript. Y. M. I. interpreted and reviewed statistical analysis of the data. Y. K. supervised the work, designed the research, interpreted data and wrote the manuscript. All authors read and approved the final manuscript. There were no conflicts of interest.

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