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Combined intake of caffeine and low-dose glucose to reduce exercise-related hypoglycaemia in individuals with type 1 diabetes on ultra-long-acting insulin degludec: A randomized, controlled, double-blind, cross-over trial

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Abstract

Aim: To evaluate whether caffeine combined with a moderate amount of glucose reduces the risk for exercise-related hypoglycaemia compared with glucose alone or control in adult people with type 1 diabetes using ultra-long-acting insulin degludec.

Materials and Methods: Sixteen participants conducted three aerobic exercise sessions (maximum 75 min) in a randomized, double-blind, cross-over design. Thirty minutes before exercise, participants ingested a drink containing either 250 mg of caffeine + 10 g of glucose + aspartame (CAF), 10 g of glucose + aspartame (GLU), or aspartame alone (ASP). The primary outcome was time to hypoglycaemia.

Results: There was a significant effect of the condition on time to hypoglycaemia ($\chi^2 = 7.674$, $p = .0216$). Pairwise comparisons revealed an 85.7% risk reduction of hypoglycaemia for CAF compared with ASP ($p = .044$). No difference was observed between GLU and ASP ($p = .104$) or between CAF and GLU ($p = .77$). While CAF increased glucose levels during exercise compared with GLU and ASP (8.3 ± 1.9 mmol/L vs. 7.7 ± 2.2 mmol/L vs. 5.8 ± 1.4 mmol/L; $p < .001$), peak plasma glucose levels during exercise did not differ between CAF and GLU (9.3 ± 1.4 mmol/L and 9.1 ± 1.6 mmol/L, $p = .80$), but were higher than in ASP (6.6 ± 1.1 mmol/L; $p < .001$). The difference in glucose levels between CAF and GLU was largest during the last 15 min of exercise ($p = .002$). Compared with GLU, CAF lowered perceived exertion ($p = .023$).

Andreas Melmer and Christoph Stettler contributed equally to this work.

Conclusions: Pre-exercise caffeine ingestion combined with a low dose of glucose reduced exercise-related hypoglycaemia compared with control while avoiding hyperglycaemia.

KEYWORDS
caffeine, clinical trial, exercise intervention, hypoglycaemia, randomized trial

1 | INTRODUCTION

Current guidelines for individuals with type 1 diabetes recommend insulin adaptation and/or the intake of additional carbohydrates before exercise to reduce the risk of exercise-related hypoglycaemia.[1] Adequate adaptation of basal insulin before exercise may be challenging for people with type 1 diabetes using the highly convenient and effective ultra-long-acting basal insulin analogues. This may particularly hold true in the context of shorter exercise duration, as in typical leisure activities. While the intake of additional carbohydrates is often the chosen strategy in this situation, this may be associated with the unwelcome consequences of hyperglycaemic excursions and weight gain.[1,2]

Alternative approaches to stabilize glucose throughout and after exercise for people using ultra-long-acting insulins encompass the ingestion of fructose[3] as an alternative carbohydrate, which is independent of insulin, the implementation of high-intensity exercise bouts,[4] or the application of pre-exercise glucagon.[5] However, they may not be unrestrictedly applicable, as fructose may be too sweet for some individuals, high-intensity bouts cannot be integrated into all exercise modalities, and glucagon bears the risk of nausea and hyperglycaemia. Therefore, widely available, easily applicable, and well-tolerated alternatives to reduce the risk of exercise-related hypoglycaemia in people using ultra-long-acting basal insulins would still be welcome.

Caffeine has been shown to moderately stimulate hepatic glucose production, reduce peripheral glucose uptake by the skeletal muscle and increase lipolysis, all of which may potentially be favourable mechanisms to stabilize glucose during exercise in people with type 1 diabetes.[6,7] The potential of caffeine in this population so far was explored in a single study of people with type 1 diabetes, revealing a smaller exercise-related decline in blood glucose following the ingestion of caffeine. While these important results clearly pointed towards the potential of caffeine in reducing exercise-related hypoglycaemia, generalizability was limited because of the lack of a control group and the study setting with rather high baseline glucose values before exercise.[8]

The present study aimed to investigate whether the ingestion of caffeine in combination with a limited amount of glucose reduces the risk for hypoglycaemia in a time-to-event analysis during a standardized session of recreational aerobic exercise in adult people with type 1 diabetes using ultra-long-acting basal insulin analogues.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

In this prospective, three-arm, cross-over, randomized, double-blinded clinical study with placebo and comparator controls, we recruited 16 adults with type 1 diabetes using insulin degludec between February 2022 and January 2023. The study was conducted at the Department of Diabetes, Endocrinology, Clinical Nutrition & Metabolism at the Bern University Hospital, Bern, Switzerland, from February 2022 until March 2023. Inclusion criteria were type 1 diabetes of at least 1 year duration with C-peptide levels <100 pmol/L, glycated haemoglobin <8.5%, age between 18 and 55 years, and use of the ultra-long-acting insulin degludec (Novo Nordisk A/S) as basal insulin for a minimum of 3 months. Key exclusion criteria were a body mass index ≥30 kg/m^2, concomitant medication interfering with glucose homeostasis, and current pregnancy. To minimize variability and optimize standardization we used the same basal insulin for all participants. Insulin degludec was chosen because of its ultra-long action and stable pharmacokinetic properties, thereby imposing a reproducible and substantial challenge to the exercise situation.[9] The full list of inclusion and exclusion criteria is presented in Appendix S1. The present study was reviewed and approved by the Ethical Committee of the Canton of Bern (dossier ID 2021-01492) before recruitment. The clinical trial was registered at Clinicaltrials.gov under the unique identifier NCT04671043.

2.2 | Study procedures

At baseline, participants arrived at the study centre after a 10-h overnight fast for a medical examination. Anthropometric measures (height, weight) were taken using an electronic ultrasound scale, and body composition was measured by electrical bioimpedance (InBody Europe). A fasting blood sample was taken for the analysis of glycated haemoglobin and C-peptide. Beta human chorionic gonadotrophin was measured in female participants of childbearing potential. A cardiopulmonary exercise test was conducted using an electronically braked cycle ergometer with breath-by-breath spirometry (COSMED Omnia) to determine the maximum oxygen uptake (VO_{2max}). Afterwards, participants were equipped with a continuous glucose monitor (CGM) device (Dexcom G6) according to the manufacturer's

instructions. Using CGM, the glucose concentrations were measured over 72 h preceding the upcoming exercise session. Participants were then randomly assigned following simple randomization procedures (using a computed-generated sequence), by an independent investigator who was not otherwise related to the study, to receive one of three possible drinks before the upcoming exercise session: 250 mg of caffeine mixed with 10 g of glucose and 10 g of aspartame (CAF), 10 g of glucose and 10 g of aspartame (GLU), or 10 g of aspartame (ASP), all diluted in 250 millilitres of water. ASP was used to cover differences in flavour between conditions. Drinks were prepared by the independent investigator and stored in a fridge in an opalescent flask until used. After 72 h, participants were re-invited to the study centre after a 10-h overnight fast. Data from the CGM system were obtained before the experiment to detect nocturnal or morning hypoglycaemia, which would have led to the postponement of the subsequent exercise session by at least 48 h, and until 24 h after the experiments to evaluate post-experiment nocturnal glucose control. Blood glucose was then titrated between 5.0 and 9.0 mmol/L using an intravenous infusion of insulin aspart (Novo Nordisk) and/or glucose 20% (Bichsel). After blood glucose remained stable (±0.2 mmol/L change every 5 min) for at least 15 min without need of further adaptations, participants ingested their assigned drink within 5 min. After a subsequent resting period of 5 min, each participant conducted up to 60 min of cycling on an electronically braked cycle ergometer at 50% of their VO_{2max}. Blood glucose was measured in venous samples every 5 min using a stationary point-of-care glucometer (Biosen C-line; EKF Diagnostics). If hypoglycaemia occurred (defined as blood glucose <3.9 mmol/L), exercise was stopped, and the participant was given oral carbohydrates until stabilization. If blood glucose was between 4.0 and 4.5 mmol/L at 60 min of exercise, exercise was prolonged by 15 min to a maximum of 75 min in total. After at least 72 h of rest, exercise sessions 2 and 3 were conducted identically to exercise session 1, but with the other drinks, according to randomization.

2.3 | Statistical analysis

The primary endpoint was time to hypoglycaemia (defined as a plasma glucose level <3.9 mmol/L) during exercise. Additional endpoints were based on plasma glucose metrics during exercise (change from baseline at time of intervention [T0] to end of exercise, mean and peak concentrations, and incidence of hypoglycaemic events). Further, we evaluated substrate oxidation and lactate levels during exercise as well as glucose control in the night following the experiment (based on sensor glucose). For the primary outcome, interventions were compared using Cox mixed-effect models. For all other outcomes, the interventions were compared using linear mixed-effect modelling. In case of a significant treatment effect (assessed using Wald χ^2-squared tests), marginal means were compared pairwise using the Tukey method for p-value adjustment. Values of $p < .05$ were considered statistically significant. Results are presented as mean ± SD unless otherwise specified. Please refer to supplementary paragraph 1 in Appendix S1 for a detailed description of the statistical methods and sample size calculation procedures used. The datasets generated during and/or analysed in the current study are available from the corresponding author upon reasonable request.

TABLE 1 Baseline characteristics of study participants.

Characteristics	Total, n = 16
Age, years	30.4 ± 8.9
Sex, female, male; n	5, 11
Body weight, kg	73.8 ± 9.7
BMI, kg/m^2	24.1 ± 2.4
HbA1c, mmol/mol (%)	8.4 ± 4.3 (64.8 ± 23.2)
Years since diagnosis of type 1 diabetes, years	18.7 ± 8.3
Basal insulin dose, IU/24 h	28.2 ± 22.3
Total daily insulin dose, IU/24 h	69.4 ± 90.4
Baseline use of insulin aspart, n (%)	6 (37.5)
Baseline use of insulin faster aspart, n (%)	5 (31.3)
Baseline use of insulin lispro, n (%)	1 (6.3)
Baseline use of insulin glulisine, n (%)	4 (25.0)
VO_{2max}, ml/min/kg	35.7 ± 4.8

Note: Data are presented as mean ± standard deviation for normally distributed data and as median [interquartile range] for non-normally distributed data, unless otherwise specified.
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; IU, international units; VO_2, oxygen uptake.

3 | RESULTS

Sixteen participants completed the study as per protocol. Table 1 reports the baseline characteristics of the study participants. Table 2 reports glucose metrics during exercise, and Table 3 reports levels of exertion and metabolic parameters during exercise. Figure 1 shows the plasma glucose profiles of each treatment arm before, during and after exercise. Table S1 in Appendix S1 reports adverse events observed during the study, and Table S2 in Appendix S1 reports nocturnal glucose trajectories after the experimental visits. Table S3 in Appendix S1 reports the CONSORT 2010 checklist. The CONSORT flow diagram is shown in Figure S1 in Appendix S1. Figure S2 in Appendix S1 shows individual time courses of plasma glucose during the experimental visits.

After the ingestion of CAF, two participants experienced hypoglycaemia during exercise. This is compared with four participants in GLU and eight participants in ASP (in these participants, hypoglycaemia occurred after a mean of 80 ± 0 min, 100 ± 6 min and 73 ± 21 min, for CAF, GLU and ASP, respectively). In the analysis of the primary outcome, we found a significant effect of the condition on the time to hypoglycaemia ($\chi^2 = 7.674$, $p = .0216$). Pairwise comparisons between the conditions revealed a lower hazard ratio for CAF compared with ASP ($p = .044$), which translates to an 85.7% reduction in the risk of hypoglycaemia. No significant difference was

TABLE 2 Plasma glucose metrics before and during exercise (N = 16)

Parameters	CAF	GLU	ASP	*p*-Value overall effect	*p*-Value CAF vs. GLU	*p*-Value CAF vs. ASP	*p*-Value GLU vs. ASP
$Glucose_{Exercise\ start}$, mmol/L	8.7 ± 1.3	8.7 ± 1.5	5.9 ± 1.2	**<.001**	.995	**<.001**	**<.001**
$Glucose_{Peak}$, mmol/L	9.3 ± 1.4	9.1 ± 1.6	6.6 ± 1.1	**<.001**	.801	**<.001**	**<.001**
Delta $Glucose_{Baseline\ -\ Exercise\ Start}$, mmol/L	2.6 ± 0.9	2.5 ± 0.7	0.0 ± 0.6	**<.001**	.825	**<.001**	**<.001**
Mean $Glucose_{Exercise}$, mmol/L	8.3 ± 1.9	7.7 ± 2.2	5.8 ± 1.4	**<.001**	**<.001**	**<.001**	**<.001**
$Glucose_{Exercise\ End}$[a]	7.7 ± 2.2	7.0 ± 2.4	5.3 ± 1.5	**<.001**	**.002**	**<.001**	**<.001**
Delta $Glucose_{Baseline\ -Exercise\ End}$, mmol/L	1.3 ± 2.1	0.5 ± 1.8	−0.75 ± 1.0	**<.001**	.151	**<.001**	**.010**

Note: Data are presented as mean ± SD for normally distributed data and as median + interquartile range for non-normally distributed data. An alpha-level of ≤.05 was considered statistically significant. Bold areas indicate statistically significant changes.
Abbreviations: ASP, aspartame; CAF, caffeine + glucose + aspartame; GLU, glucose + aspartame; VO_2, oxygen uptake.
[a]Calculated over the last 15 min of exercise.

TABLE 3 Levels of exertion and metabolic parameters during exercise (N = 16)

Parameters	Caffeine mean ± SD	GLU mean ± SD	ASP mean ± SD	*p*-Value overall effect	*p*-Value CAF vs. ASP	*p*-Value CAF vs. GLU	*p*-Value GLU vs. ASP
BORG rating of perceived exertion	11.4 ± 1.3	12.1 ± 2.0	12.1 ± 1.4	**.025**	.312	**.023**	.386
Lactate during exercise, mmol/L	2.1 ± 1.1	1.7 ± 1.1	1.6 ± 0.9	**<.001**	**<.001**	**<.001**	.207
VO_2 during exercise, ml/min/kg	22.7 ± 3.8	22.6 ± 3.9	22.2 ± 3.7	**.015**	.093	**.006**	.460

Note: Data are presented as mean ± SD. Statistically significant differences are highlighted in bold.
Abbreviations: ASP, aspartame; CAF, caffeine + glucose + aspartame; GLU, glucose + aspartame; SD, standard deviation; VO_2, oxygen uptake.

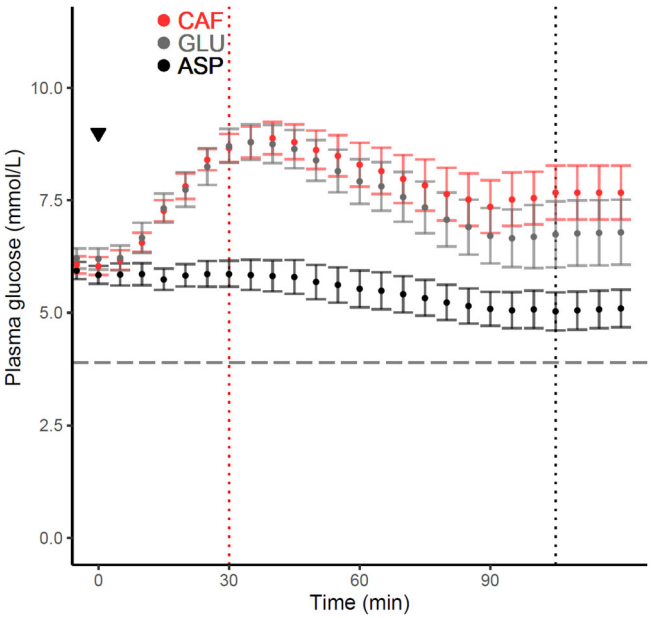

FIGURE 1 Exercise-related glucose profiles. Figure 1 shows the glucose profile of each treatment arm. Black triangle marks the intake of the respective blinded drink at timepoint 0. Red dashed line indicates the start of the exercise (t30), black dashed line indicates the end of the exercise (t105). ASP, aspartame; CAF, caffeine + glucose + aspartame; GLU, glucose + aspartame.

observed between GLU and ASP ($p = .104$) or between CAF and GLU ($p = .77$).

In the 30 min before the start of exercise (i.e. from the intake of the respective blinded drink at t_0 until the start of exercise), CAF and GLU resulted in a similar increase in plasma glucose (2.6 ± 0.9 mmol/L and 2.5 ± 0.7 mmol/L, $p = .83$). Further, peak plasma glucose levels during exercise were not significantly different following CAF and GLU (9.3 ± 1.4 mmol/L and 9.1 ± 1.6 mmol/L, respectively; $p = .80$), but both were higher than in ASP (6.6 ± 1.1 mmol/L; both $p < .001$).

On average, CAF increased glucose levels during exercise as compared with GLU and ASP (8.3 ± 1.9 mmol/L vs. 7.7 ± 2.2 mmol/L vs. 5.8 ± 1.4 mmol/L; both $p < .001$). Of note, the difference between CAF and GLU was largest towards the end of the exercise, with mean glucose levels of 7.7 ± 2.2 mmol/L for CAF vs. 7.0 ± 2.4 mmol/L for GLU over the last 15 min ($p = .002$).

In comparison with GLU, the BORG rating of perceived exertion was reduced after ingestion of CAF (11.4 ± 1.3 vs. 12.1 ± 1.4; $p = .023$). Plasma concentrations of lactate during exercise were higher following the ingestion of CAF as compared with GLU and ASP (2.1 ± 1.1 mmol/L vs. 1.7 ± 1.1 mmol/L vs. 1.6 ± 0.9 mmol/L; both $p < .001$). No significant differences in substrate oxidation during exercise were observed. No significant treatment effect on overnight glucose control following the experiment was observed. Insulin doses in the titration period did not differ across interventions ($p = .705$).

4 | DISCUSSION

In the present study in adult people with type 1 diabetes using ultra-long-acting basal insulin degludec, we evaluated the efficacy of a combined ingestion of caffeine plus a limited amount of glucose compared with glucose alone or a control condition. The main findings were fivefold: (a) caffeine plus glucose, but not glucose alone, significantly reduced the risk of hypoglycaemia during exercise compared with control; (b) caffeine combined with glucose increased glucose levels during exercise compared with glucose alone or control, but without any significant differences between the conditions in peak glucose levels and without causing hyperglycaemia; (c) the observed difference in glucose levels between the combined ingestion of caffeine and glucose versus glucose alone was largest towards the end of exercise; (d) while performed power was identical in all experimental sessions, perceived exertion was lower with caffeine and glucose versus glucose alone; and (e) lactate levels were higher after intake of caffeine and glucose compared with glucose or control.

Taken together, these findings indicate that caffeine may allow people with type 1 diabetes using ultra-long-acting basal insulin degludec to reduce the amount of exogenous glucose required to maintain euglycaemia during aerobic exercise of limited duration, as is typically performed in a recreational context. The 10 g of glucose used in the present study were considerably lower than the general recommendations given in guidelines for exercise situations when reduction of insulin is not possible (i.e. up to 90 g).[1] While sufficient intake of carbohydrates before and during exercise is, on the one hand, protective against hypoglycaemia, the caloric load may also be counterproductive if weight management is the reason for working out, as may often be the case in such activities.[10] Moreover, higher doses of glucose may translate into exercise-related hyperglycaemia, which when repeated, will interfere with the long-term goals of diabetes management.[11] Of note, even in the present study with a rather low dose of glucose, hyperglycaemia at least transiently occurred in four participants, irrespective of whether caffeine or glucose alone was ingested (see Figure S2 in Appendix S1). This indicates that amounts of glucose even in the lower range of current treatment recommendations may already exceed the individual requirements during recreational exercise in people with type 1 diabetes, further emphasizing the need for individualized treatment decisions in the context of exercise. In the present approach, combining caffeine with a limited amount of glucose resulted in plasma concentrations that were in a desirable range, avoiding hyperglycaemia while still minimizing the risk of hypoglycaemia. In particular, caffeine induced a more sustained stabilization of glycaemia towards the end of exercise when compared with glucose alone.

Interestingly, the ingestion of caffeine has previously been shown to augment the symptomatic and hormonal responses to hypoglycaemia in people with[12,13] and without[14] type 1 diabetes.

While the present study did not assess the symptoms associated with hypoglycaemia, and given that the exercise situation might have interfered with such an assessment anyway, the single dose of 250 mg of caffeine used in this study, corresponding to approximately three cups of espresso, was well tolerated during exercise, with no caffeine-associated adverse events (please refer to Table S1 in Appendix S1). Of note, following a position paper by the International Society of Sports Nutrition, the caffeine dose used in the present study is rated as moderate.[15]

An interesting notion in the present study is that caffeine intake translated into a lower rating of perceived exertion during exercise. This is in line with previous reports showing antagonistic actions of caffeine on the adenosine A1 and A2 receptors in the central nervous system, which increase alertness but decrease perceived exertion during exercise.[16,17] In addition, caffeine has been shown to stimulate calcium release from the sarcoplasmic reticulum, enhance contraction power in muscle fibres, and ultimately facilitate exercise movements.[18,19] While we would refrain from overemphasizing this finding, lower perceived exertion may increase motivation when performing physical activity, thereby supporting regular participation in exercise or increasing the duration of exercise sessions. Motivation is a recognized barrier to training activities for people both with and without type 1 diabetes, preventing many from reaching recommended exercise targets.[20–22]

The finding of increased lactate levels after ingestion of caffeine may be related to the increased adrenergic response, increasing both lipolysis and glycogenolysis. Consumption of caffeine before exercise has been linked previously to an increased availability of exercise-related substrates, including lactate,[23,24] with moderate elevations of lactate serving both as a direct energy source as well as a precursor molecule for gluconeogenesis in the liver and the working muscle.[23,25]

The effect of caffeine on long-term glucose control in people with type 1 diabetes has been previously studied by other researchers[26,27] and lies outside the scope of the present work. Nevertheless, we did not observe any differences in nocturnal glucose control after the experiments; thus, our data do not provide evidence for a detrimental effect of a single intake of caffeine before exercise on subsequent glucose control.

We acknowledge the following strengths and limitations: To our knowledge, this is the first randomized controlled trial to compare the effects of caffeine added to a limited amount of glucose with glucose alone and with a control intervention in a carefully designed approach. Omitting a 'caffeine-only arm' in favour of combining the smallest amount of glucose recommended in guidelines with caffeine may enhance the practicability and acceptance of the present approach and application in the daily routine by people with type 1 diabetes. The exercise performed in the present study (50% VO_{2max} for 60-75 min) is a realistic example of recreational exercise, thereby applying to a substantial number of people with type 1 diabetes. We acknowledge that we did neither control for chronic habitual caffeine consumption nor genetic polymorphisms influencing the ergogenic response of caffeine during exercise, both factors potentially reducing true effects. On the other hand, the controlled design, with each participant serving as their own control, may limit this effect. In addition, when considering the potential variation in individual elimination half-lives for caffeine, the present study will probably underestimate the effect of caffeine on glycaemia, particularly in people with slow

metabolism.[28] The study investigated a comparably small group of young and non-obese participants with a male preponderance, limiting the generalizability of the present results in particular to people with obesity, type 2 diabetes, or elderly people. Furthermore, the present study did not include people with cardiovascular disease, and caution is advised when evaluating the use of caffeine in such circumstances. Future and larger-scale studies will also have to investigate whether the effects found in the present study are confirmed when adding a caffeine-only intervention arm or by gradually increasing the caffeine dose within the recommended range (i.e. 3-6 mg of caffeine per kg of body mass). Future studies may include different exercise scenarios (e.g. higher or lower intensity, longer duration) and differing baseline blood glucose concentrations.

In summary, pre-exercise ingestion of a moderate amount of caffeine combined with a limited dose of glucose reduced exercise-related hypoglycaemia compared with control by modestly increasing plasma glucose levels during exercise, stabilizing glycaemia towards the end of exercise, and avoiding hyperglycaemia. Caffeine induced an increase of lactate during exercise, which is metabolically of potential benefit, while reducing the rate of perceived exertion, thereby potentially further reducing barriers towards an implementation of regular physical exercise for people with type 1 diabetes.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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