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A method for evaluating the risks of glucose dysregulation in daily life by continuous measurement of glucose excursions under reduced glycemic load: a pilot study

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Introduction: Continuous glucose monitoring is essential for the management of patients with metabolic syndromes in their daily lives. However, how metabolic risks are accessed using time-series glucose excursion data for healthy individuals remains unclear.

Methods: Thus, this study aimed to present a method for evaluating the risks of glucose dysregulation by analyzing glucose responses under reduced glycemic load using a phytochemical alpha-glucosidase inhibitor. A 14-day pilot trial with healthy adult participants was conducted to demonstrate the validity of the method.

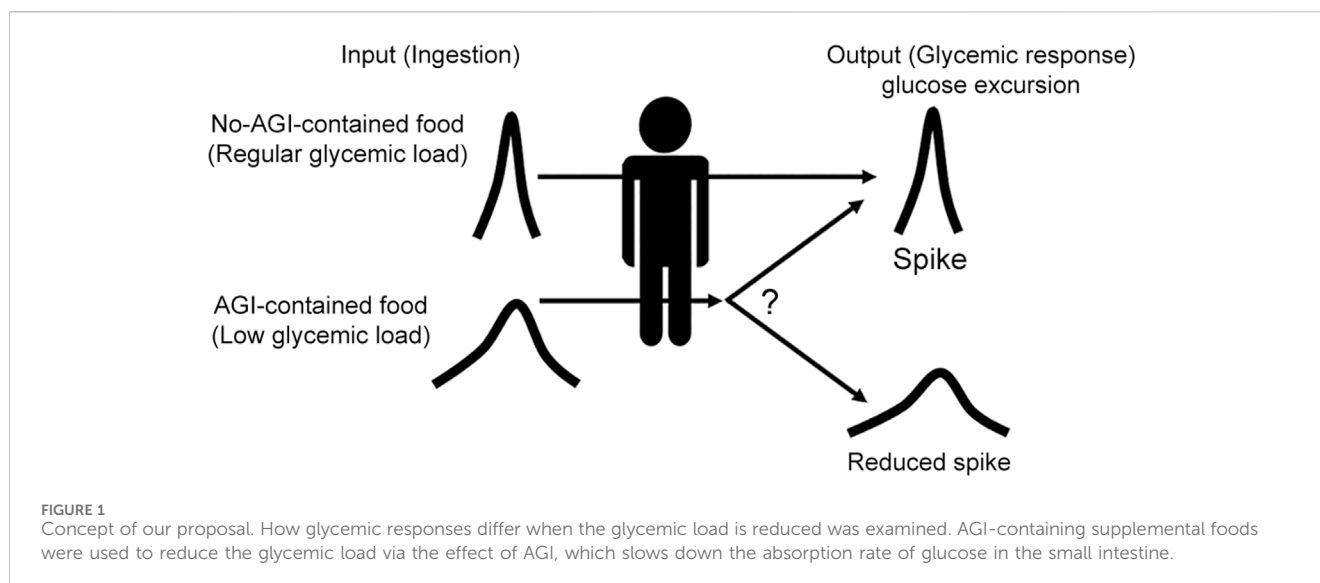
Results and Discussion: The results showed that ultradian glucose spike packets with lower heights dominantly appeared under reduced glycemic load, replacing postprandial single-lobe glucose spikes with higher heights. Furthermore, the frequency dominance of ultradian spike packets contributed to the reduction of overall mean glucose excursions during the test period under reduced glycemic load. Based on the time-delay model, it was indicated that glycemic load reduction recovers regular glucose–insulin coupling accompanying ultradian oscillations, thereby contributing to the maintenance of glucose homeostasis. The findings of this study indicate that the frequency ratio between pulsatile spike packets and single-lobe spikes could be a marker for evaluating glucose regulation/dysregulation in healthy adults.

KEYWORDS

continuous glucose monitoring, glucose homeostasis, metabolic risk management, glucose spike, pulsatile glucose oscillation, glucose excursion

1 Introduction

Recently, wearable continuous glucose monitoring (CGM) systems have become widespread (Villena Gonzales et al., 2019; Zafar et al., 2022). Their validity has been demonstrated in individuals with diabetes mellitus who need optimal glycemic control (Langendam et al., 2012; Chan, 2017; Lawton et al., 2018; Cappon et al., 2019). The benefits of using CGM systems are not limited to the clinical field. Recently, great interest has been focused on the daily use of CGM systems by healthy individuals. This is due to their potential benefits in maintaining their physiological states via optimal control of diets and



sleep, not only for the management of personalized health but also for achieving the best performance in sports (Jospe et al., 2020; Holzer et al., 2022; Keshet et al., 2023; Klupa et al., 2023; Wang et al., 2023; Freckmann et al., 2024).

CGM systems can provide consecutive time-series data on glucose excursions during daily life. Such data, even acquired in a limited short term, involve beneficial information such as postprandial hyperglycemia and subsequent reactive hypoglycemia (Zecchin et al., 2016; Freckmann et al., 2018; Yu et al., 2019). This advantage compensates for traditional pinpoint glycemic tests, including the oral glucose tolerance test (OGTT). CGM systems can provide versatile information involving neurophysiological activities that are not limited to conventional dietary glucose responses. A key to using the original features of CGM systems is to assess the time-series data. Notably, the criteria for evaluating the extent of dysregulation of glucose metabolism in individuals without diabetes mellitus remain unclear due to insufficient data for such healthy individuals with potential metabolic risks. Some attempts have been made referring to the diagnostic criteria for diabetes mellitus, which potentially leads CGM users to suboptimal behaviors, including unnecessary dietary restriction with a risk of undernutrition (Guess, 2023).

Therefore, a machine learning (ML)-based approach has been developed to extract abnormal patterns of glucose responses during daily life (Seo et al., 2019; Woldaregay et al., 2019; Mujahid et al., 2021; Alhaddad et al., 2022). This approach is advantageous for extracting useful information from large-scale data, although the underlying physiological mechanisms remain unclear. However, the ML-based approach has a limitation in that the machines cannot explain causal associations in their answers. This may become problematic if the answers are ineffective. Thus, explainable artificial intelligence has attracted much attention to overcome this problem (Nor et al., 2021; Chaddad et al., 2023; Duckworth et al., 2024).

Another approach has been developed by postulating a simple hypothesis. A previous study proposed and demonstrated a method for detecting glucose dysfunction in healthy

individuals by classifying three glucotypes (high, medium, and severe glucose-variability phenotypes). These types were successfully classified by analyzing consecutive glucose excursion data acquired in daily life using ML techniques, and the assessments were consistent with conventional glycemic tests such as OGTT (Hall et al., 2018). The validity of this method has been independently demonstrated in another previous study (Breschi et al., 2021).

In this study, we propose a more explainable method for evaluating the risk of individualized glycemic dysregulation in daily life via CGM measurements under reduced glycemic load conditions. We hypothesized that, with a reduction in glycemic load, glycemic dysfunction would be readily recovered for lower-risk individuals, whereas dysregulation would remain for higher-risk individuals. This method evaluates the characteristic glucose dynamics associated with glycemic regulation/dysregulation to identify higher-risk individuals. Figure 1 shows the concept of the proposed method.

This study aimed to demonstrate the validity of the proposed method by conducting a 14-day pilot trial with healthy young and middle-aged healthy adult participants. For this purpose, we prepared small supplemental foods containing an alpha-glucosidase inhibitor (AGI) to generate low-glycemic load conditions. AGI has been reported to moderate glucose absorption in the small intestine by inhibiting alpha-glucosidase, which is involved in the breakdown of polysaccharides (like maltose) into glucose (Fang et al., 2017; Dong et al., 2021; Liu et al., 2021). Using such small supplemental foods is expected to help examine how dynamics are affected by glycemic load reduction from usual levels while maintaining usual diets and eating habits.

The characteristic glucose dynamics associated with glucose homeostasis and its disruption were extracted from the individualized time-series CGM data acquired over the three 14-day test periods. A model for explaining how our method can predict the potential risk of glycemic dysfunctions from the dynamic patterns of CGM traces in daily life was provided by correlating the data with clinical parameters.

TABLE 1 Specifications of the foods used in the study represented by the content per ingestion.

| Description | Test-food A (AGI-contained food) | Test-food B (nonAGI food) |
|--------------|----------------------------------|---------------------------|
| Carbohydrate | 16.8 g | 25.8 g |
| Energy | 67.2 kcal | 103.2 kcal |
| Salacinol | 0.089 mg | 0 mg |

2 Materials and methods

2.1 Ethics

Written informed consent was obtained from all participants before participation in this study. The study protocol was reviewed and approved by the Research Ethics Committee of the School of Engineering, The University of Tokyo (Approval No. KE22-34), and the Ethics Committee of the Kobe University Graduate School of Health Sciences (Approval No. 1124). Furthermore, the study protocol was officially registered with the UMIN Clinical Trials Registry (UMIN000051003) and is publicly accessible at <https://www.umin.ac.jp/ctr/index.htm>. All experiments were performed in accordance with the Declaration of Helsinki.

2.2 Participants

Healthy daytime workers aged 20–75 years with a high school graduate level in manufacturing companies were recruited by advertisement with a leaflet invitation to the study. The exclusion criteria included individuals who took medications acting on glucose

metabolism, such as steroids, nonsteroidal antiinflammatory drugs, and antidiabetic drugs, those with HbA1c > 6.1% and body mass index >35 who needed treatment, and those who were at risk of subcutaneous bleeding by inserting a CGM sensor. Consequently, 17 participants (age: 45.8 ± 12.3 years), including 7 females, were included in this study.

2.3 Test-food preparation and overall experimental design

Salacia reticulata was used to prepare test foods containing AGI. *Salacia reticulata* involves salacinol as a phytochemical AGI, whose effect on reducing blood sugar has been demonstrated by many previous studies (Sim et al., 2010; Medagama, 2015; Morikawa et al., 2015; Stohs and Ray, 2015), including clinical trials with healthy/patient (mainly type 2 diabetes mellitus) participants (Collene et al., 2005; Heacock et al., 2005; Williams et al., 2007; Radha and Amrithaveni, 2009; Koteswar et al., 2013; Kushwaha et al., 2016; Vyas et al., 2016). Baked confectioneries containing *S. reticulata* were provided as snack foods containing AGI (Test-food A). Furthermore, baked confectioneries without *S. reticulata* were provided as regular snack foods (Test-food B). Table 1 shows the specifications of the experimental test samples.

A single-arm trial consisting of four study sessions was designed to test our proposal (Figure 2A). The first session (Session 1) was a 3-day nonintervention session, maintaining normal eating activities with unchanged diet quality. The second session (Session 2) was a 4-day regular snack session with Test-food B twice a day. The third session (Session 3) was a 4-day snack session with Test-food A. The fourth session (Session 4) was a 3-day session with Test-food A ingested with three meals.

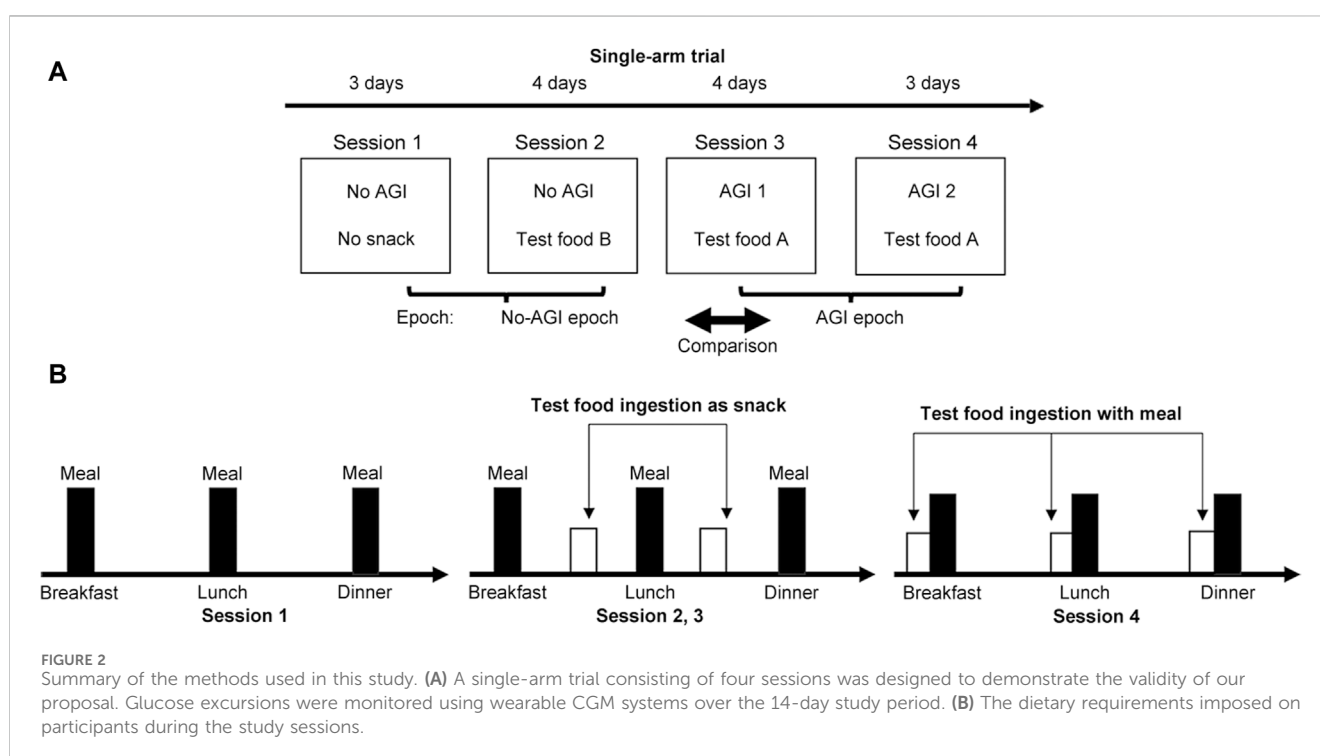


TABLE 2 Total ingestion amounts of components involved in the test food per day during each session epoch.

| Epoch | Session 2 | Session 3 | Session 4 |
|--------------------------------------|-----------|-----------|-----------|
| Additional carbohydrate (g) | 51.6 | 33.6 | 50.4 |
| Additional energy (kcal) | 206 | 134 | 202 |
| Assumed energy increase rate (%) | 8.7 | 5.6 | 8.5 |
| Total AGI (Salacinol) ingestion (mg) | 0 | 0.178 | 0.267 |

The total test period was 14 days. The participants were asked to complete these sessions in accordance with the study instructions (Figure 2B). In Session 1, all participants were asked to eat their main meals three times a day while avoiding irregular snacking. In Session 2, participants were asked to consume interprandial Test-food B twice a day as a regular snack between breakfast and lunch and between lunch and dinner. In Session 3, participants were similarly asked to consume interprandial Test-food A as an AGI-containing snack food. Finally, in Session 4, participants were asked to take Test-food A with the three meals. Ingestion of any other snack food was strictly prohibited throughout the four sessions. Furthermore, the ingestion of any food containing corn syrup was strictly prohibited during the study period because syrup nullifies the effect of AGI.

Participants wore CGM sensors during the test period. The CGM data were analyzed afterward. The individual baseline was evaluated from the CGM data acquired in Sessions 1 and 2 with no foods containing AGI, considering the two possible eating habits with and without snacking in the usual life. In Session 3, Test-food A containing AGI was expected to reduce the glycemic load, thereby reducing glucose excursions. In Session 4, AGI was expected to exert more inhibitory effects on glucose excursions.

The effects of additional ingestion of test foods on individual glycemic regulation were evaluated to obtain reliable data. The additional energy by ingestion was 207 kcal at most per day (Table 2). This might affect the daily diet by an 8.7% increase at most. Furthermore, whether this energy increase by ingesting test foods could disturb glycemic regulation was examined by setting a checkpoint between Sessions 3 and 4. The test was continued with participants who showed no signs of glycemic dysfunction in Sessions 1 and 2 by checking their CGM data.

Participants were asked to maintain their food choices during the test sessions to eliminate health-conscious bias effects. Notably, participants were asked during the test period not to consume foods containing glucose syrup, which avoids the effect of AGI. Participants were also asked to keep their own time-stamped diet records during the study to confirm whether the experiments would be successfully completed with no health-conscious bias.

2.4 CGM measurement

To complete the test trial, we required a wearable CGM system that could operate continuously for 14 days. For this, we selected a commercially available CGM system (Freestyle Libre Pro, Abbot Diabetes Care Inc., United States, Japanese pharmaceutical approval: 22800BZX00227,000). This system consisted of a sensor attached to the upper arm. Plasma glucose levels translated from

intercellular fluid were recorded every 15 min for 14 days. No data were missed as long as the CGM sensor was correctly attached (Tang et al., 2020). Although the sampling rate was fixed at 4 cycle/h (every 15 min), it provided sufficient data for the analysis of glucose excursions of >30 min (corresponding to 2 cycle/h) based on the conventional sampling theorem.

2.5 Data analysis

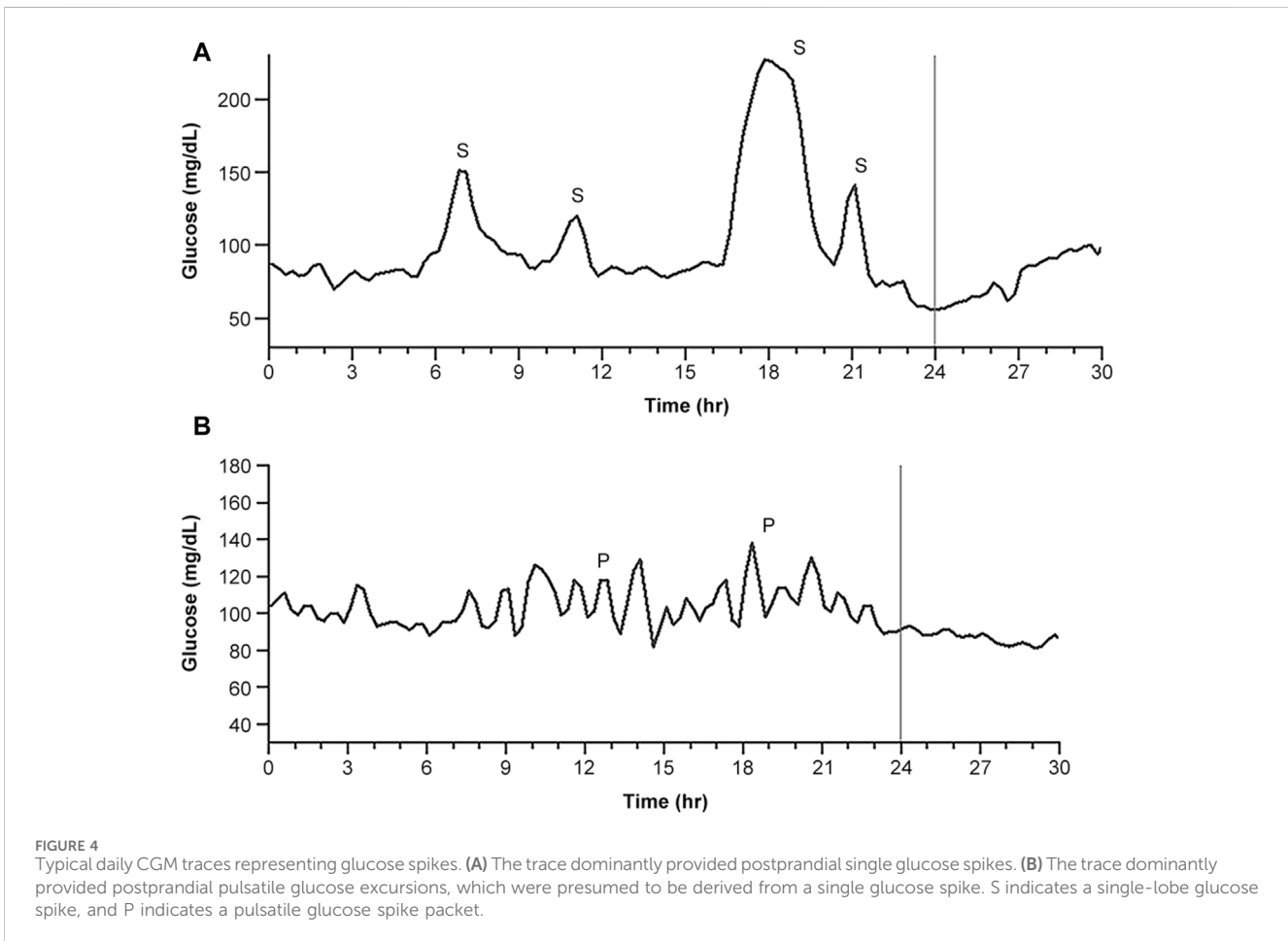
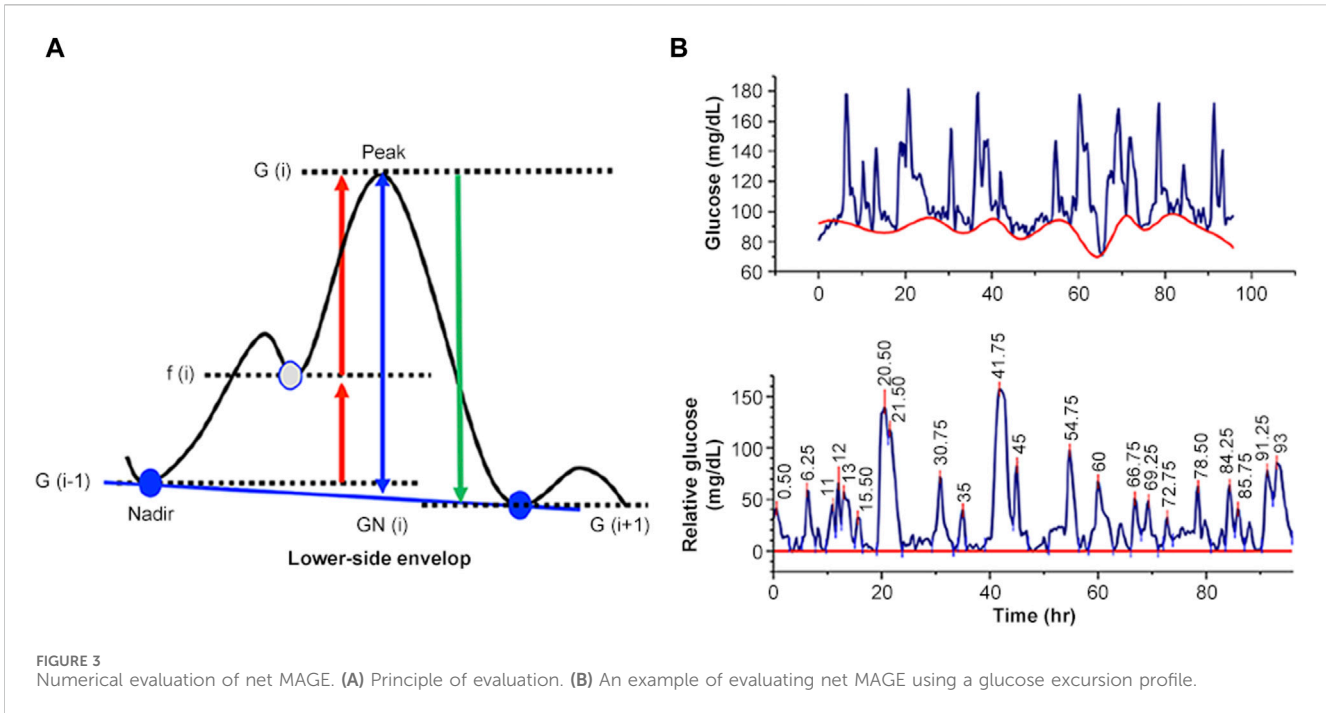
2.5.1 Net mean amplitude of glucose excursion (MAGE)

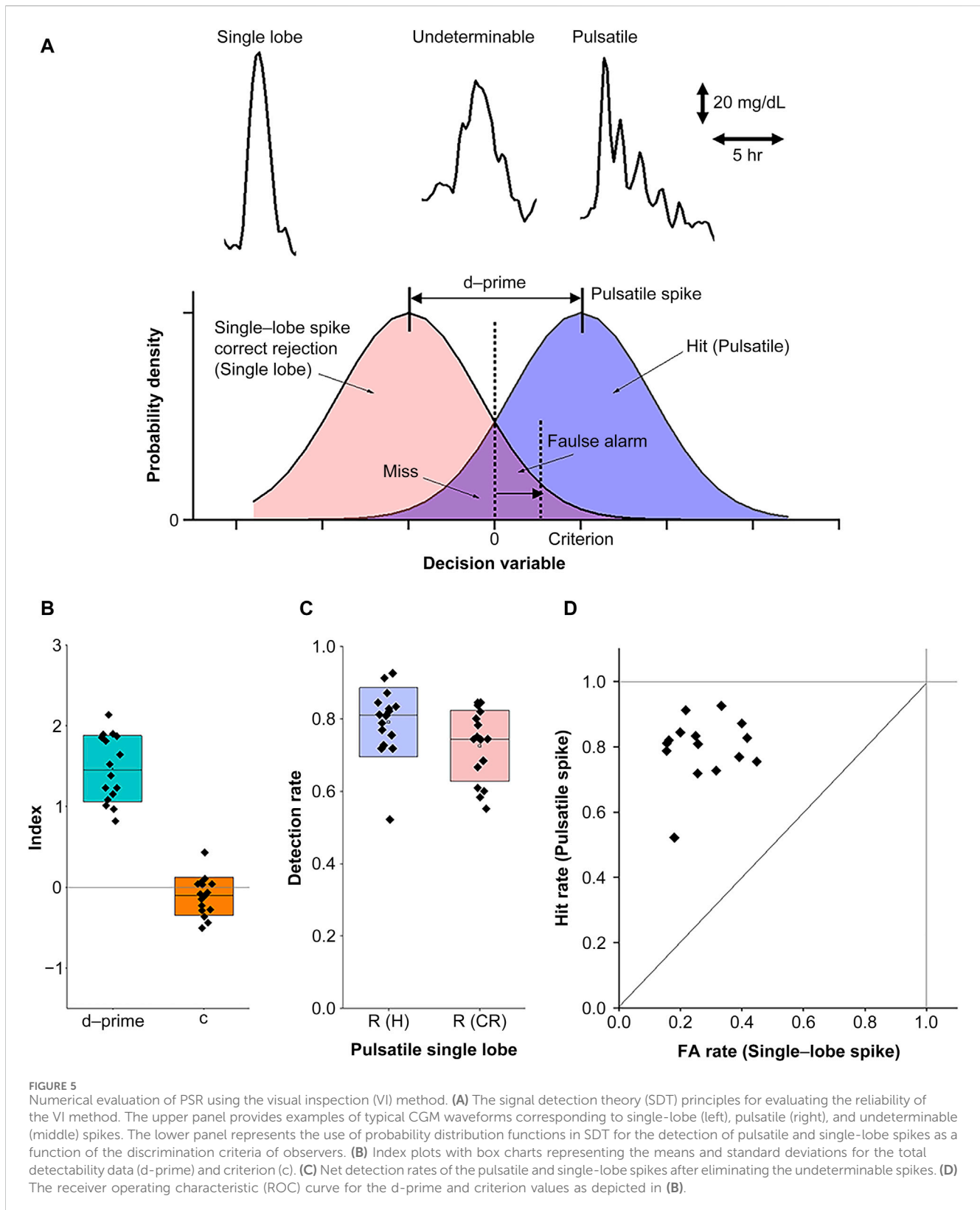
The MAGE is often used to numerically evaluate daily glucose excursions. The MAGE is the average of upward (MAGE+) and downward (MAGE-) excursions exceeding the standard deviation of glycemic excursion data over a day measured by CGM as follows:

$$MAGE = (MAGE_+ + MAGE_-)/2$$

The MAGE can be systemically derived from a series of peaks and nadir levels extracted from glycemic excursion profiles measured by CGM (Marling et al., 2011). Glycemic excursion fluctuations can be evaluated using the upper and lower envelopes of the excursion profiles. Therefore, net glycemic fluctuation amplitudes defined for each glycemic peak as $|G(i) - GN(i)|$ were introduced. Such a net glycemic fluctuation amplitude can be readily derived from the glycemic peaks and lower envelopes of glycemic excursions (Figure 3A). Here, the peaks and nadirs were detected by utilizing the automatic peak-search function with secondary-differentiation processing provided by the software (OriginPro 2021b; OriginLab Corporation, Northampton, MA, United States). The lower envelopes derived from the detected nadirs were taken as baselines and used to evaluate the net amplitudes of the detected peaks. These were regarded as the net MAGE in place of conventional MAGE. An example of the approximation applied to a measured glycemic excursion is shown in Figure 3B. Glucose excursions for each session were characterized using the average net MAGE of all detected peaks.

We evaluated individual net MAGE as a function of HbA1c. A regression analysis was conducted based on a conventional analysis of variance (ANOVA) to investigate whether these parameters were correlated. We then evaluated the individual basal net MAGE as a reflection of the measures in the daily lives of the participants, taking into account the net MAGE for Sessions 1 and 2 to minimize any confounding effect of snacking on glucose excursions. Using these individual basal net MAGE, we determined the difference between the relative net MAGE and the basal net MAGE for each session as Δ net MAGE. To simply evaluate the effect of AGI ingestion on net





MAGE, we combined the data from Sessions 3 and 4 as the AGL-ingestion session and evaluated the session difference Δ_{net} MAGE. The statistical significance was tested with a one-sample t -test. The Δ_{net} MAGE was depicted as a function of HbA1c. A regression analysis based on ANOVA was performed.

2.5.2 Characterization of the postprandial glucose excursion pattern

In the current study, two types of postprandial glucose increase were observed: single-lobe spike (Figure 4A) and pulsatile glucose excursion (Figure 4B). Pulsatile excursion, which may be derived

from a single-lobe glucose increase, was considered, and the pulsatile spike noted by P was counted while identifying the single-lobe glucose spike as S.

All postprandial glucose excursions in the CGM traces for each session were classified. The ratio of the number of single-lobe and pulsatile spikes (PSR) emerging in each session was defined as follows:

$$PSR \equiv \frac{\text{Number of pulsatile spike}}{\text{Number of single-lobe spike}}$$

The PSR for the session with no AGI was defined as PSR1, and that for the session with AGI was defined as PSR2. Furthermore, a ratio γ was defined as follows:

$$\gamma \equiv PSR2/PSR1$$

Because the PSR increases, the pulsatile spikes become more dominant. The ratio γ indicates the effect of AGI on the promotion of pulsatile spikes while suppressing single-lobe spikes.

Here, the PSR evaluation was performed by visual inspection (VI), with single-lobe spikes identified as isolated large peaks and pulsatile spikes identified as a series of periodic small peaks. To avoid the risk of discrimination errors due to observer bias inherent in this VI method, we used signal detection theory (SDT) to determine the validity of the method. SDT provides a numerical framework for evaluating the detection of signals as distinct from noise (Decarlo, 2020) while separately assessing any cognitive bias of observers (Jayakumar and Simpson, 2020; Locke and Robinson, 2021). While these spikes were readily distinguishable by their typical waveforms, there were also undeterminable spikes that reduced the distance between the two populations and degraded their distinguishability. SDT can separate undeterminable spikes to evaluate the net distinguishability.

As shown in Figure 5A, we assumed two Gaussian populations corresponding to the pulsatile and single-lobe spikes as a function of the VI-based discrimination criteria. According to the SDT framework, we introduce four judgment categories. These were hit (H), miss (M), correct rejection (CR), and false alarm (FA). Hs and CRs could be attributed to the reliable detection of the pulsatile and single-lobe spikes, respectively, and corresponded to each nonoverlapping portion of the population curve (in the figure, blue represents pulsatile spikes and red, single-lobe spike). In contrast, the Ms and FAs attributed to the undeterminable spikes corresponded to the overlapping portions.

The distance between the two populations, defined as d-prime, represented distinguishability, and the criteria set the threshold to determine whether the spikes belonged to the pulsatile or single-lobe group. As d-prime increased, its distinguishability improved. Criterion (c) represents observer bias, with positive and negative criteria representing prioritization of pulsatile and single-lobe spikes, respectively. These SDT parameters were calculated using the detection rates of R(H) and R(FA) as

$$d' = Z[R(H)] - Z[R(FA)]$$

$$c = -\frac{1}{2}\{Z[R(H)] + Z[R(FA)]\},$$

where Z represents the normal inverse cumulative distribution function.

We further checked d-prime and the criteria for all the data acquired in the current study. Since the Ms and FAs for the undeterminable spikes were not dissociable, we evaluated R(FA) using half of the undeterminable spike number for convenience, assuming no significant differences between the pulsatile and single-lobe populations. As shown in Figure 5B, we confirmed that d-prime differed significantly from the zero level (averaged d-prime = 1.47, SD = 0.40, $p = 3.6E-10$, power = 1), suggesting that the VI method can provide fair distinguishability. In contrast, the slightly negative criterion ($c = -0.11$, SD = 0.23) did not reach statistical significance ($p = 0.077$, power = 0.43), suggesting sufficient neutrality to exclude the possibility of observer bias. With this VI method, we achieved sufficient detectability in both pulsatile (0.79 ± 0.095 (SD)) and single-lobe spikes (0.73 ± 0.098 (SD)) for PSR evaluation (Figure 5C). Finally, we evaluated the receiver operating characteristic (ROC) curve (Figure 5D) to ensure that the IV-based discrimination was conducted according to the criterion while minimizing chance judgments. Taken together, these evaluations confirmed that the detection ratios obtained via the VI method were a reliable measure of PSR as $PSR = R(H)/R(CR)$.

2.5.3 Evaluation of the periodicity of pulsatile spikes

The CGM traces were analyzed to evaluate the net MAGE through every glycemic peak on the traces as $|G(i) - GN(i)|$. The temporal information of the peak provided each interval of the two adjacent peaks. Such intervals represent the instantaneous period of the pulsatile glucose spikes. Therefore, all intervals belonging to the glucose excursion in a session epoch were summed, and a distribution curve was depicted using the kernel density evaluation (KDE) method. Additionally, a peak interval was identified as the period of the pulsatile spikes, ranging from 60 to 120 min. The KDE peaks with longer intervals were considered to be attributed to the meal interval.

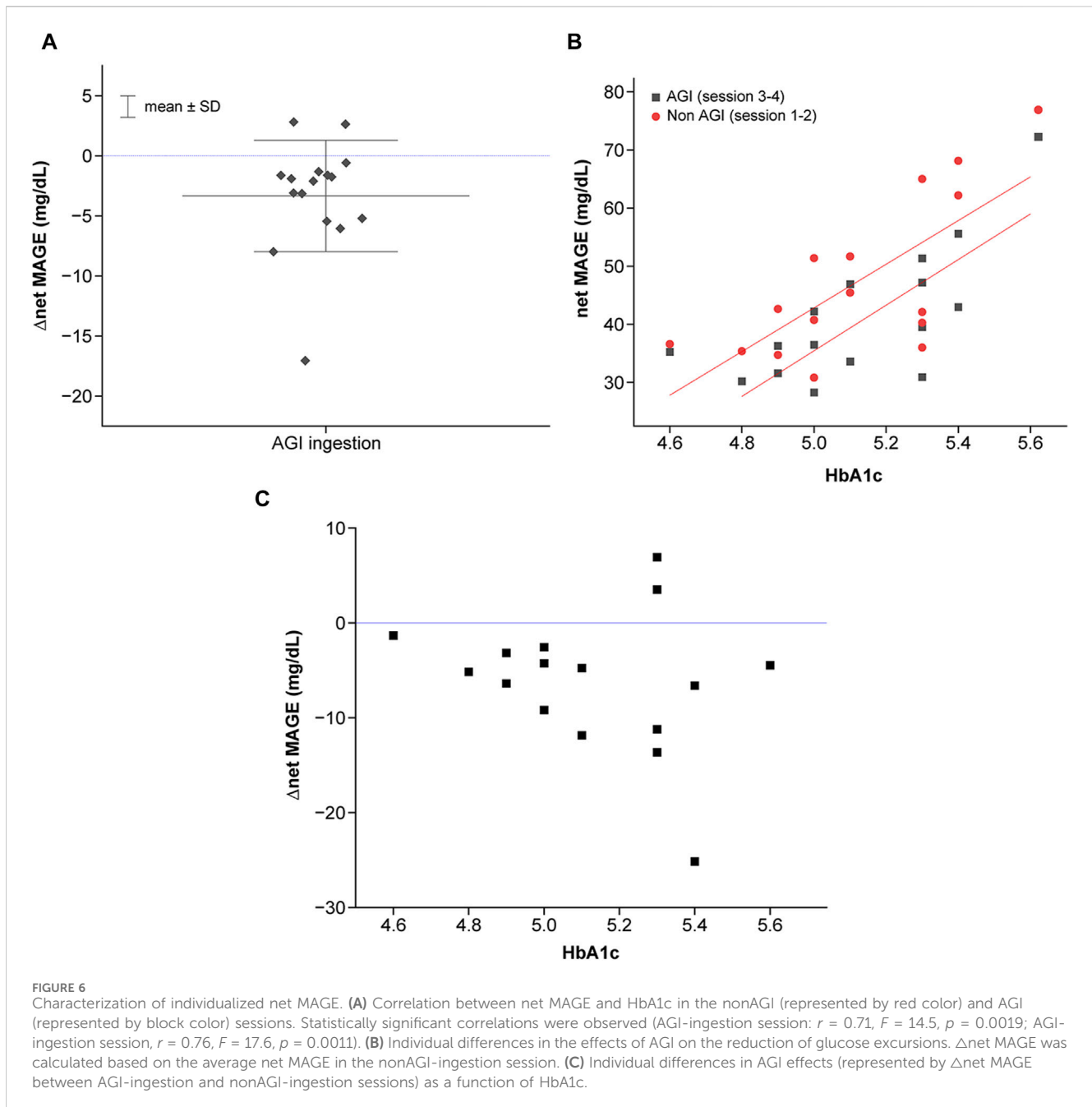
2.5.4 Statistics

Differences in net MAGE between the groups were statistically evaluated using one-way repeated measures analysis of variance (ANOVA). Correlations between two parameters were evaluated by regression analysis using Pearson's correlation coefficient (r) and p -values based on ANOVA. A p -value < 0.05 indicated statistical significance. All statistical analyses were performed using OriginPro 2021b (OriginLab Corporation, Northampton, MA, United States).

3 Results

3.1 Individualized AGI effects on glucose excursions

Although AGI ingestion overall reduced the glucose excursion, some participants showed large glucose excursions despite AGI ingestion (Figure 6A). Thus, the correlation between glucose excursion and HbA1c as a clinical parameter was investigated to clarify this individual difference (Figure 6B). A significant positive correlation was observed for nonAGI-ingestion sessions ($r = 0.71$, $F = 14.5$, $p = 0.0019$) and AGI-ingestion sessions ($r = 0.76$, $F = 17.6$,



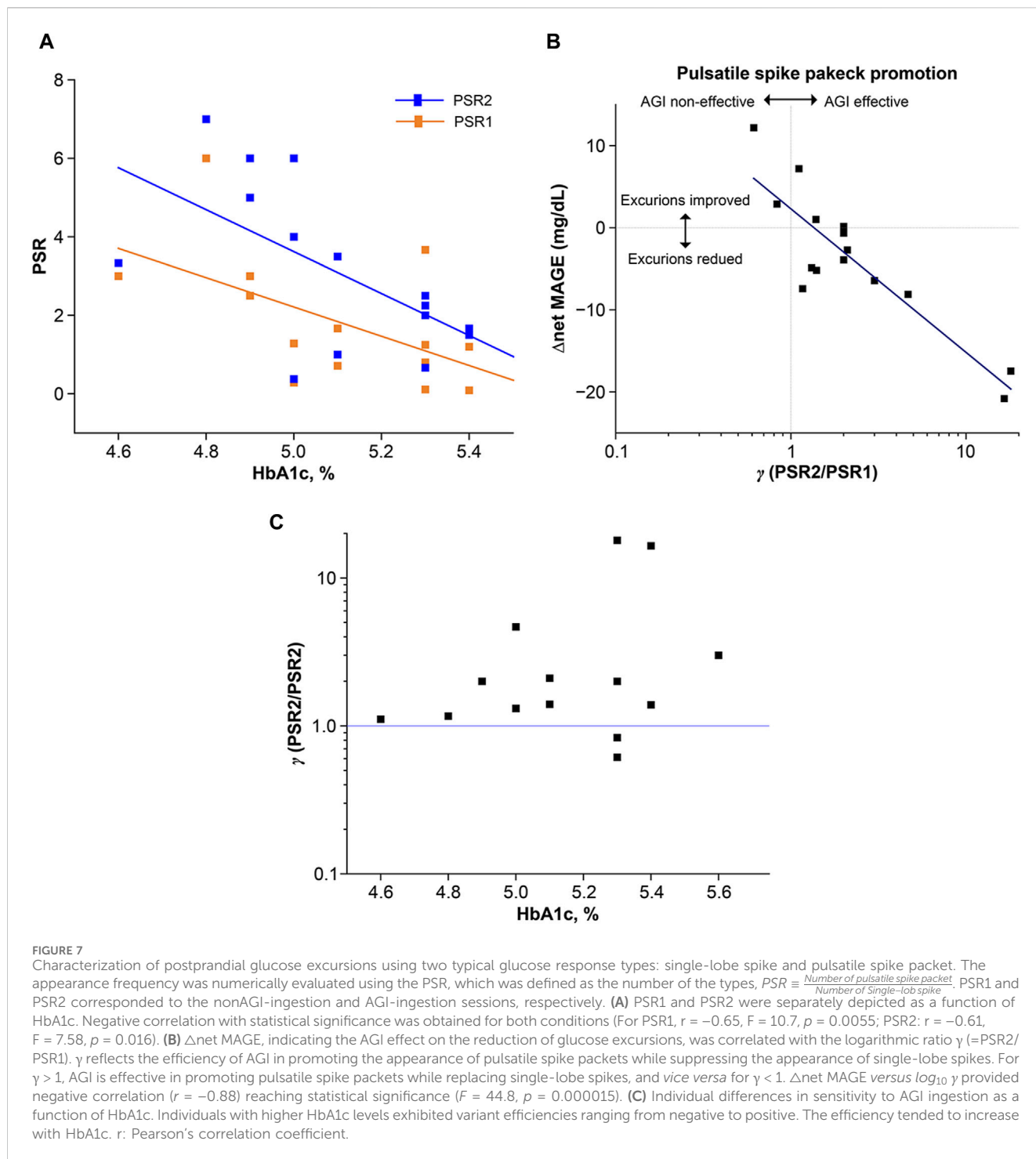
$p = 0.0011$). The correlation in the AGI session provided lower glucose excursions than that in the nonAGI-ingestion session. This indicates that AGI ingestion was generally effective for reducing glucose excursions independently of HbA1c, although glucose excursion increased with HbA1c.

However, the efficiency of glucose excursion reduction differed. The efficiency, evaluated by Δ net MAGE between the nonAGI-ingestion and AGI-ingestion sessions, showed severe individual variance for higher HbA1c levels, whereas the efficiency tended to increase with increasing HbA1c levels (Figure 6C). The variance was attributed to individuals who deviated from the tendency, some of whom ruled out AGI effects. Hence, glucose responses for individuals with higher HbA1c levels should be considered by considering two glucose response types (higher and lower sensitivities to AGI).

3.2 Temporal features of postprandial glucose responses

As described in the Methods section, two postprandial glucose response patterns, i.e., single-lobe and pulsatile spikes were observed. Both of these two types appeared in almost all CGM traces across all participants. The frequencies of the single-lobe spike and pulsatile spike packet differed with the conditions (nonAGI ingestion or AGI ingestion) and individuals. The PSR was used to examine the differences arising from the conditions and individuals.

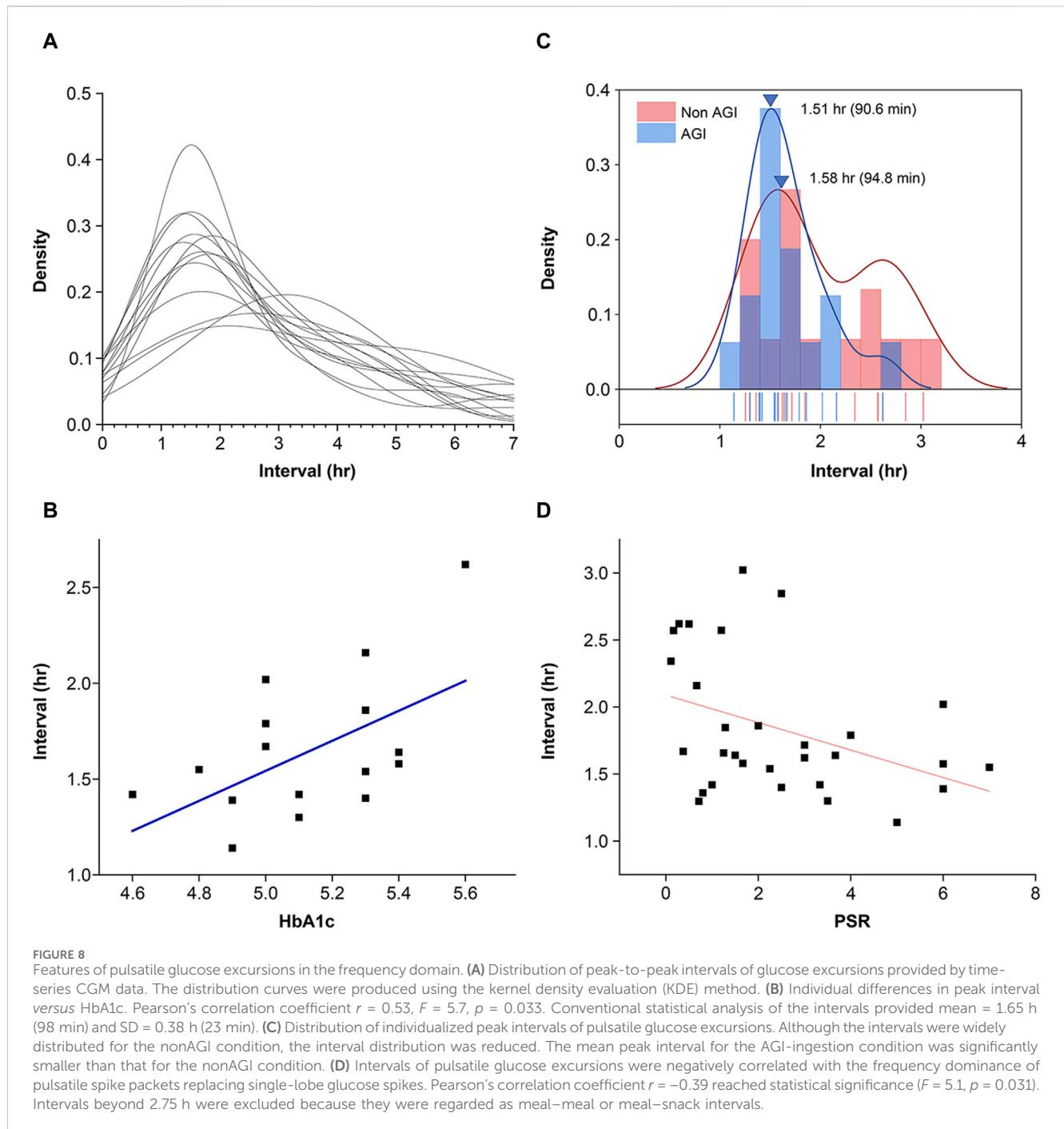
A significant negative correlation was observed between the individualized frequency ratio and HbA1c levels for both the nonAGI-ingestion session ($r = -0.65$, $F = 10.7$, $p = 0.0055$) and AGI-ingestion sessions ($r = -0.61$, $F = 7.58$, $p = 0.016$) (Figure 7A).



These findings indicate that the frequency dominance of the pulsatile spike packets decreased with increasing HbA1c levels, and the frequency dominance of the single-lobe spikes increased with increasing HbA1c levels. Despite such HbA1c dependence, the PSR for the AGI-ingestion condition always exceeded that for the nonAGI-ingestion condition, indicating the inhibitory effect of AGI on glucose excursions independently of HbA1c.

Because AGI ingestion had an impact on the reduction of glucose excursions and the increase of the frequency dominance of the pulsatile spike packets, the correlation between $\Delta\text{net MAGE}$

and $\gamma (=PSR2/PSR1)$ was examined (Figure 7B), with γ representing the AGI effect on improving the frequency of pulsatile spike packets while suppressing the frequency of single-lobe spikes. A significant negative correlation was observed between $\Delta\text{net MAGE}$ and $\log_{10} \gamma$ ($r = -0.88$, $F = 44.8$, $p = 0.000015$). This indicates that the frequency dominance of the pulsatile spike packets contributed to the reduction of postprandial glucose excursions. Furthermore, how the ratio γ reflecting the AGI was individualized using HbA1c was examined to clarify why the sensitivity to AGI individually differed (Figure 7C).



Interestingly, γ tended to increase with increasing HbA1c levels while exhibiting a large variance for higher HbA1c levels. Furthermore, the two variant cases providing $\gamma < 1$ corresponded to the two variant cases providing $\Delta_{\text{net}} \text{MAGE} > 0$ in the AGI-ingestion session. The tendency of increasing γ with increasing HbA1c levels and the negative correlation between PSR and increasing HbA1c levels appeared to be discrepant. However, upon visual inspection of all the CGM traces, the pulsatile spike packets were highly frequent for lower HbA1c levels independently of AGI ingestion, indicating that AGI did not contribute to suppressing the small-number single-lobe spikes in the AGI-

ingestion session. In contrast, AGI effectively suppressed large-number single-lobe spikes in individuals with high HbA1c levels.

3.3 Periodicity analysis of the pulsatile glucose excursion

Pulsatile spike packets as a type of postprandial glucose response were observed. Furthermore, pulsatile glucose excursions not limited to postprandial responses were observed. Hence, the pulsatile glucose excursions that appeared during the entire

session periods in the frequency domain were characterized. Thus, the distributions of peak-to-peak intervals of glucose excursions were examined.

Figure 5 shows the individualized KDE curves derived from the histograms of the intervals where the bin was set at 0.2 h. The participants provided similar KDE curves with peak intervals around 1.5 h, except for individuals who provided longer intervals beyond 2 h (Figure 8A). These longer intervals were attributed to the meal–meal interval, not pulsatile glucose oscillations. The correlation between individual intervals and HbA1c levels was investigated (Figure 8B). A significant negative correlation was observed ($r = 0.53$, $F = 5.6$, $p = 0.033$).

Glycemic load reduction by AGI ingestion was expected to shorten the intervals of pulsatile glucose spike packets. The individualized mean intervals were widely distributed for the nonAGI-ingestion condition, and the interval distributions were considerably reduced (Figure 8C). However, no significant difference in the peak interval was observed between the nonAGI- and AGI-ingestion conditions, whereas the mean interval for the AGI-ingestion condition was slightly smaller than that for the nonAGI condition. Furthermore, how the frequency dominance of the pulsatile glucose spike packets affected the pulse intervals was examined. The pulse intervals were negatively correlated with the frequency dominance of the pulsatile glucose spike packets ($r = -0.39$, $F = 5.1$, $p = 0.031$) (Figure 8D).

4 Discussion

This study demonstrated the validity of our proposed method for evaluating glucose dysregulation by CGM during a short-term test period under reduced glycemic load. The results showed that postprandial glucose excursions were divided into two types: single-lobe spike and pulsatile spike packet. The pulsatile spike packets exhibited ultradian rhythms with a mean of 98 min. Furthermore, such ultradian glucose oscillations were observed throughout the day and were not limited to postprandial glucose responses. These results showed that the observed ultradian glucose excursions, including the spike packets, could be attributed to pulsatile insulin secretion.

Many studies have revealed that insulin secretion is pulsed in two dissociable modes (Sonnenberg et al., 1992; Sturis et al., 1993). One is a fast mode with a period ranging from 5 to 15 min (Lang et al., 1979; Pørksen et al., 2002; Hollingdal et al., 2005; Pedersen et al., 2005; Schmitz et al., 2008), and the other is a slow mode with an ultradian period ranging from 50 to 150 min (Simon et al., 1987; Sturis et al., 1995; Simon, 1998; Simon and Brandenberger, 2002). These two insulin secretion modes arise from different mechanisms. The fast mode is attributed to intracellular coherent cooperation via tight junctions (Dyachok et al., 2008; Dhumpa et al., 2014; McKenna et al., 2016; Ng et al., 2021), whereas the slow mode is attributed to the glucose–insulin negative feedback system for maximizing glucose utilization (Sturis et al., 1991; Bruce et al., 2022). Because glucose and insulin are tightly coupled by this negative feedback loop, the glucose excursion reflects the ultradian insulin rhythms. Thus, the ultradian pulsatile glucose excursions, including postprandial spike packets, were thought to be caused by the above tight glucose–insulin coupling.

Ultradian pulsatile glucose excursions, including spike packets, exhibited frequency dominance by AGI ingestion while replacing single-lobe spikes. Since AGI reduces glycemic load, the frequency dominance of pulsatile glucose excursions could be attributed to this glycemic load reduction. However, the mechanism by which glycemic load reduction contributes to promoting ultradian pulsatile glucose excursions remains unclear. This may be attributed to the time-delay model (Li et al., 2006).

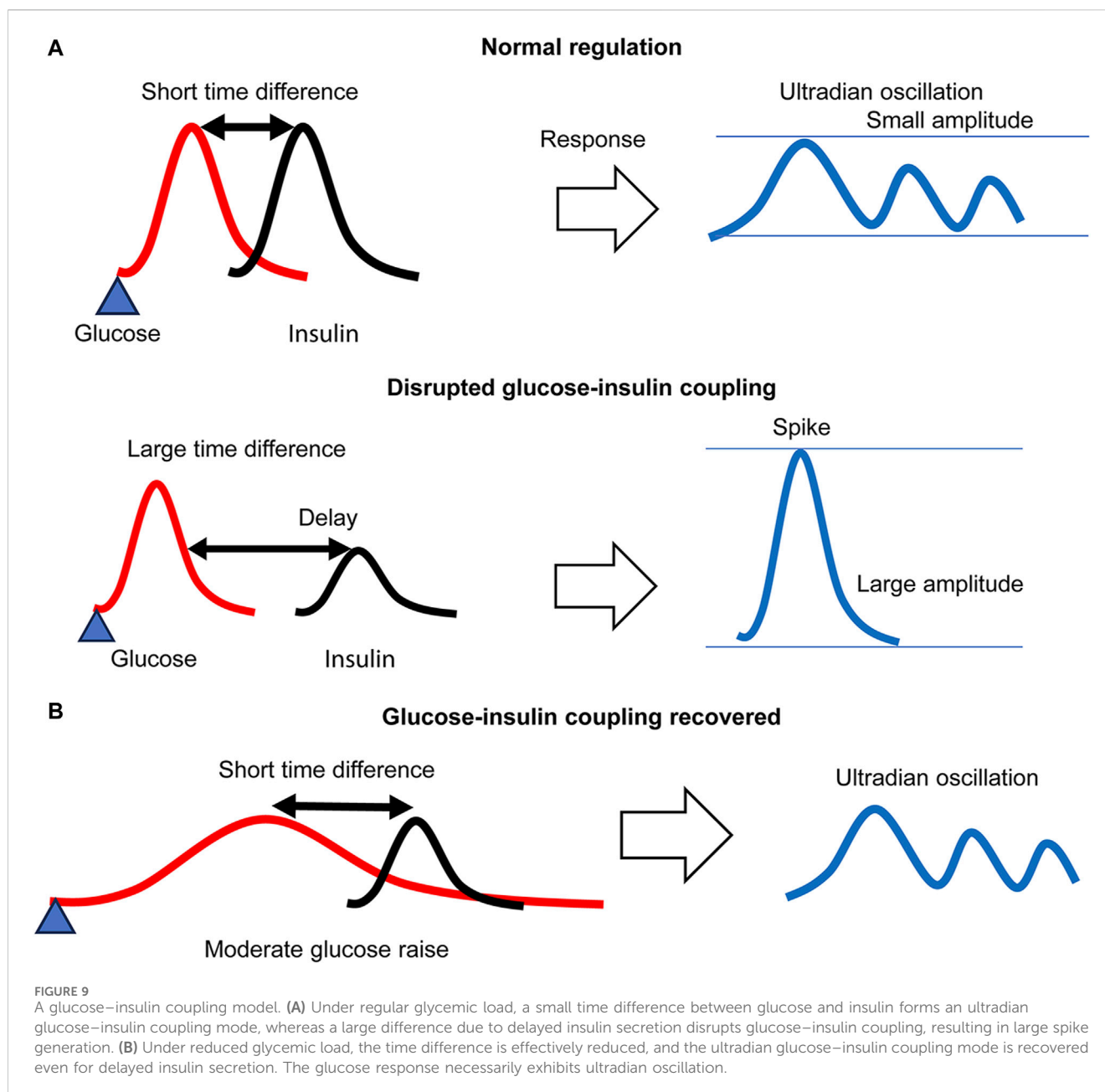
The model suggests that a large time difference between glucose and insulin generates large glucose spikes, whereas a small difference generates ultradian pulsatile glucose excursions via glucose–insulin coupling based on their native feedback loop (Figure 9A). Thus, we considered that AGI reduced the difference by reducing the glucose absorption rate, thereby achieving glucose–insulin coupling accompanied by ultradian glucose excursions (Figure 9B).

Many studies have shown that pulsatile insulin secretion not only in the fast mode (Pørksen, 2002; Pørksen et al., 2002; Satin et al., 2015; Lee et al., 2017; Laurenti et al., 2021) but also in the slow mode (O'Meara et al., 1993; Simon et al., 1994) is beneficial for maintaining glucose homeostasis. The finding of this study that frequency dominance of the pulsatile glucose spike packets contributed to reducing overall glucose excursions throughout the day by AGI ingestion may be involved in such benefits. Therefore, the PSR, defined by the number of pulsatile spike packets and single-lobe glucose spikes, could be a key parameter for evaluating the risks of glycemic dysregulation.

The purpose of our proposed method was to provide personalized risk assessments of glucose dysregulation for non-DM patients beyond the limitations of conventional clinical diagnostic criteria. This aim was in line with that of the previous studies in which the concept of glucotypes was presented (Hall et al., 2018; Breschi et al., 2021). These studies argue for the validity of using the glucotypes for such personal assessments and consider whether glucotype classification is more informative than average glucose levels (Hulman et al., 2021).

Our finding that net MAGE is positively correlated with HbA1c is not very informative. However, we also found that the appearance ratio for pulsatile *versus* single-lobe spikes exhibited large variability at the higher end of the HbA1c range, suggesting that the ratio may reflect glucose dysregulation levels. Furthermore, the ratio was greatly improved in those with higher HbA1c by glycemic load reduction via AGI ingestion. This indicates that individual glucose responses may be dynamic and change in accordance with glycemic load. As such, it may provide a more useful measure than HbA1c. This finding in the present study diverges most from the focus of previous glucotype research.

The proposed method has some limitations. One is highlighted by the existence of individuals showing null effects of AGI on reducing their glucose excursions. Causes of elevated glucose levels include stress hormones associated with not only insulin-independent endocrine systems but also the central nervous system, such as cortisol (Ortiz et al., 2019; Bentele et al., 2021; Ouyang et al., 2022). Further studies are needed to explore the mechanism by which glycemic dysregulation occurs in such individuals. Another limitation is highlighted by the validity of AGI in reducing the glycemic load. The results showed that the period of ultradian excursions increased with increasing HbA1c levels, suggesting that the AGI effect diminished with increasing HbA1c levels.



This is explainable by the fact that an increase in HbA1c levels reflects the risk of glucose dysregulation that may obstruct glucose–insulin coupling. Nevertheless, some individuals with even higher HbA1c levels improved ultradian glucose excursions by AGI, suggesting that AGI is expected to recover degraded glucose–insulin coupling for higher HbA1c levels. However, in this study, the maximum HbA1c level of the participants was 5.6%, which was within the normal range (4.6–6.0%). Further studies with individuals with much higher HbA1c levels (5.8–6.4%) are needed.

Another limitation was that we did not measure insulin and glucose simultaneously. Insulin resistance is a crucial risk factor for diabetes mellitus (DM). Hyperinsulinemia is a marker for metabolic dysfunctions, including insulin resistance (Ward et al., 1990; Dankner et al., 2009; Thomas et al., 2019), suggesting that

hyperinsulinemia may be placed upstream of insulin resistance (Janssen, 2021). Thus, the progression of metabolic dysfunction can be evaluated by monitoring both insulin and glucose, which is why simultaneous insulin–glucose measurement is of great importance and provides greater benefits not only for DM patients but also those in the preclinical stages of DM (Meigs et al., 2020). Future studies should address this issue further, and this will be aided by the ongoing development of wearable insulin monitoring devices (Sabu et al., 2019; Liu et al., 2022; Psoma and Kanthou, 2023).

An issue we have not clarified in this study is the mechanism by which glycemic load reduction causes ultradian pulsatile glucose excursions. Recent research suggests that insulin oscillations regulate cellular energy metabolism via the AKT–insulin pathway in the frequency domain (Kubota et al., 2012; Purvis and Lahav,

2012; Kubota et al., 2018). Whether ultradian oscillations can be explained by such molecular mechanisms must be determined by future studies.

In conclusion, this study provides a simple method for evaluating the risks of glucose dysregulation from time-series data acquired by a wearable CGM system. This method analyzes data obtained during regular daily life while ingesting supplemental foods containing AGI to reduce the overall dietary glycemic load. The results showed that AGI effects on daily glucose excursions provided frequency-dominant pulsatile glucose spike packets with lower peaks, replacing single-lobe spikes with higher peaks. The analysis of the glucose excursion data in the frequency domain revealed that the pulsatile glucose spike packets were involved in ultradian glucose oscillation, which is an index to show the health of glucose–insulin homeostasis. The proposed method evaluates how glucose dysregulation is recovered by reducing the glycemic load during daily life. This method provides information that is much different from that of traditional tests conducted under higher glycemic load, compensating for them.

Many studies have used wearable CGM sensors to examine glucose excursions in the daily lives of healthy individuals and determine their potential as a tool with which to evaluate the risk of type-2 DM. However, these studies have only evaluated postprandial glucose excursions, and the data obtained is discussed in terms of the standard features of a conventional glucose–insulin response. Consequently, personal assessments tend to be based on the criteria used for diagnosis (Stefan et al., 2015; Taylor et al., 2019; Nguyen et al., 2020; Bermingham et al., 2023).

In contrast, our method of evaluating glucose excursions in relation to ultradian rhythms enables a more precise investigation of individual glucose dysregulation away from homeostasis (Asher and Zhu, 2023). There is growing evidence that glucose homeostasis is regulated not only by the simple glucose–insulin axis but also by complex nonlinear systems that respond to a wide variety of factors, including neurophysiological (Singh et al., 2018; Yaribeygi et al., 2022), genetic (Partch et al., 2014; El-Athman et al., 2019; Bonnefond and Semple, 2022), and epigenetic (Zheng et al., 2015; Maude et al., 2021; Wu et al., 2023) variables, as well as neurotransmitters such as serotonin (Paulmann et al., 2009; Ohara-Imaizumi et al., 2013). This study has highlighted the importance of developing a precise and individualized medical approach to DM (Chung et al., 2020; Franceschi, 2022). We hope that our method will contribute to this.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

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Ethics statement

The studies involving humans were approved by the study protocol was reviewed and approved by the Research Ethics Committee of the School of Engineering, The University of Tokyo (Approval No. KE22-34), and the Ethics Committee of the Kobe University Graduate School of Health Sciences (Approval No. 1124). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YK: Writing–original draft, Writing–review and editing. HO: Writing–review and editing. KK: Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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