# Spectral Structure and Nonlinear Dynamics Properties of Long-Term Interstitial Fluid Glucose

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**Abstract:** The spread of continuous indwelling sensors in the subcutaneous tissue has enabled continuous monitoring of interstitial fluid glucose concentration (ISFG) under daily activities. This technology is considered to enable the development of a method for evaluating glycemic control function by analyzing not only the detailed state of diabetes and other pathological conditions but also the characteristics of glycemic dynamics. To clarify the basic fluctuation characteristics of long-term ISFG, the spectral structure and nonlinear dynamics properties of ISFG obtained by continuous monitoring for 11 days were analyzed in healthy and diabetic subjects.

Key words: Blood glucose, diabetes, heart rate variability, interstitial fluid glucose, spectral analysis.

# 1. Introduction

According to the 9<sup>th</sup> edition of International Diabetes Federation (IDF) Diabetes Alas 2019, it was estimated that in 2017 there are 451 million (age 18-99years) people with diabetes worldwide [1]. The number of adults living with diabetes have been more than tripled over the past 20 years. Diabetes is one of the fastest growing health challenges of the 21st century.

As a new way to understand the pathology of diabetes, continuous indwelling sensors in the subcutaneous tissue has enabled continuous monitoring of interstitial fluid glucose (ISFG) under daily activities [2]-[6]. This technology is considered to enable the development of a method for evaluating glycemic control function by analyzing not only the detailed state of diabetes and other pathological conditions but also the altered dynamics properties of ISFG fluctuation. In order to clarify the basic fluctuation characteristics of ISFG, the frequency structure and nonlinear dynamics properties of long-term ISFG fluctuations during daily life were analyzed.

# 2. Methods

#### 2.1. Subjects

The subjects were eight men (age,  $51 \pm 13$  yr) including two patients with type 2 diabetes mellitus (Table 1). All of them gave written informed consent to participate this study. The protocol of this study was approved by the Ethics Review Committee of Nagoya City University Graduate School of Medical Sciences and Nagoya City University Hospital (No. 60-18-0211).

Table 1. Subjects' Characteristics					
Variable	Healthy	Diabetes			
Age, yr	48 ± 10	61 ± 15			
Mean ISFG, mg/dL	101 ± 6	158 ± 13			

#### 2.2. Procedures

We used a FreeStyle Libre Flush system (Abbot Diabetes Care, Alameda, CA, USA) for continuous monitoring of ISFG. The ISFG sensor was inserted on the back of the upper arm and ISFG was measured continuously every 15 min for 11 days. The data were uploaded to a personal computer from a FreeStyle Libre Reader as a text file.

### 2.3. Data Analyses

To determine the frequency structure of long-term continuous ISFG for 11 days, 1024-point fast Fourier transformation (FFT) was performed. Briefly, the ISFG time series were interpolated with a step function, resampled at 1024 equidistant time points, filtered with a Hanning window, and converted into frequency domain by FFT.

To analyze the nonlinear dynamics properties of long-term continuous ISFG, scaling exponents were calculated by detrended fluctuation analysis (DFA) [7]. This measure quantifies the correlation properties of fractal-like dynamics of glycemic control [8], [9]. The scaling exponents were defined separately for scaling regions of 1 to 2 hours, 2 to 6 hours, 6 to 12 hours, and > 12 hours as  $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$ , and  $\alpha_4$ , respectively. The exponents range between 0.5 and 1.5; values close to 0.5 indicate the dynamics is White-noise-like uncorrelated random sequence, values close to 1.5 indicate Brown-noise-like strongly correlated inflexible sequence, and values around 1.0 indicate fractal-noise-like moderately correlated and so-called "regulated" sequence. Increased  $\alpha$  for a time scale of 2 to 24 hours has been reported as a characteristic of diabetes in an earlier study of 24-hour continuous ISFG monitoring [8].

# 3. Results

The average ISFG over 11 days was  $101 \pm 6 \text{ mg/dL}$  and  $158 \pm 13 \text{ mg/dL}$  for healthy and diabetic subjects, respectively. The power spectra of long-term ISFG fluctuation in healthy and diabetic subjects are presented in Fig. 1 and 2, respectively. Among healthy subjects, the spectral peaks of fluctuations with periods of 24 hours or longer were observed as the highest peaks in 5 out of 6 subjects. The second and third highest peaks were observed at frequencies corresponding to periods of 12, 8, and 6 hours; peak for 12 hours was the second or third highest in 3 out of 6 subjects and peak for 8 hours was in all healthy subjects (Fig. 1). In two diabetic subjects, peak for 8 hours was the highest. Although peaks for  $\geq 24$ , 12, and 6 hours were observed, they were the second or third highest peaks.

The results of DFA of long-term ISFG dominant are presented in Fig. 3 and Table 2. The scaling exponents in healthy subjects revealed that the dynamics in time scale between 1 and 2 hours was Brown-noise-like strongly correlated fluctuation, showing an exponent >1.5. Whereas, the dynamics between 2-6 hours ( $\alpha_2$ ), 6-12 hours ( $\alpha_3$ ), and  $\geq$ 12 hours ( $\alpha_4$ ) were fractal-noise-like moderately correlated sequences, showing a exponent between 0.5 and 1.5. In diabetic subjects, the dynamics between 1 and 2 hours was also Brown-noise-like strongly correlated fluctuation ( $\alpha_1 > 1.5$ ) and the dynamics between 2-6 hours ( $\alpha_2$ ) and 6-12 hours ( $\alpha_3$ ) were fractal-noise-like moderately correlated sequences, showing a exponent between 0.5 and 1.5. The dynamic  $\geq$ 12 hours ( $\alpha_4$ ) in diabetic subjects was, however, White-noise-like uncorrelated random sequence, showing an exponent <0.5.



#### 4. Discussions

Using a FreeStyle Libre Flush system, we monitored ISFG continuously for 11 days and analyzed the spectral structure and nonlinear dynamics properties of the long-term fluctuation. The power spectra showed multiple peaks at frequencies corresponding to >24-, 24-, 12-, 8-, and 6-hour periods in both healthy and diabetic subjects. While the peaks of 24-hour or longer periods were dominant components of long-term ISFG in healthy subjects, the dominant component in diabetic subjects was a fluctuation of 8-hour period. Consistent with this observation, the DFA revealed that ISFG dynamics in diabetic subjects was White-noise-like random sequence for scaling region  $\geq$ 24 hours, while it was fractal-noise-like moderately correlated sequences in healthy subjects. Because this is a pilot study with a limited sample size, no definitive conclusion can be drawn. This study, however, suggests that the long-term continuous monitoring of ISFG may provide the dynamic properties of glucose regulations and their pathophysiology that have not been known from discontinuous or shorter observations of glucose level.







Fig. 3. Detrended fluctuation analysis of long-term ISFG.

Table 2. Scaling Exponents of ISFG Dynamics					
Scaling Region	1-2 hours	2-6 hours	6-12 hours	≥12 hours	
and Exponent	α1	α2	α3	α4	
Healthy	1.51 ± 0.16	$1.21 \pm 0.12$	$0.94 \pm 0.08$	$0.64 \pm 0.14$	
Diabetes	$1.75 \pm 0.08$	$1.36 \pm 0.17$	$0.86 \pm 0.06$	$0.42 \pm 0.12$	
					-

To our knowledge, this is the first studies to examine the frequency structure and/or nonlinear dynamics of long-term continuous ISFG fluctuation over a week. Although there are many studies on the complexity or fractality of ISFG dynamics using DFA, monitoring length in most studies was a single day (24 hours) [8], [10]-[12]. These earlier studies of 24-hour ISFG reported the multifractality of dynamics, i.e., the presence of multiple slopes in DFA curve [8], [10]. Ogata *et al.* [8] performed DFA for 24-hour ISFG and found a crossover point in DFA curve at around 2 hours in healthy subjects; the scaling exponent was >1.5 below this point, but between 0.5 and 1.5 above that point. In diabetic subjects, however, the crossover point was around 3 hours and the exponent remained >1.5 even above that point. Similar findings were reported by Varela *et al.* [10], who demonstrated that increased time to the crossover point predicted risk for the development of type 2 diabetes (1.53 times hazards risk for every 30 min delay in crossover point). Because a scaling exponent >1.5 indicates positively correlated glucose dynamics, a larger exponent below the crossover point implies that monotonous increase or decrease in ISFG persists during the period, such as those typically observed during 2 hours after meals. It is reasonable that this duration is extended in subjects with impaired glucose tolerance or diabetes. In the present study, we observed a greater scaling exponent for scale region of 1 to 2 hours than for 2 to 6 hours, indicating the presence of a crossover point

around 2 hours. Also, the exponents in both regions ( $\alpha_1$  and  $\alpha_2$ ) were greater in diabetic than healthy subjects. These observations are consistent with those in the earlier studies of 24-hour ISFG.

In the present study, however, we also observed further decreases in scaling exponents in the regions of longer time scales, indicating additional multifractality for the time scale over several hours. Particularly, while the average exponent for >12 hours ( $\alpha_4$ ) was 0.64 in healthy subjects, it was 0.42 in diabetic subjects. This indicates that the ISFG in diabetic subjects was uncorrelated random sequence, suggesting that glucose regulations in diabetes may be impaired (not regulated) in the time scales of around one day or longer. These observations are thought to be the results that can be achieved only by continuous monitoring over 10 days, but the sample included only two diabetic subjects. These observations should be confirmed in future studies.

# 5. Conclusion

In this pilot study with a small sample size, we observed that long-term ISFG fluctuation over 11 days shows power spectrum with multiple peaks at frequencies corresponding to >24-, 24-, 12-, 8-, and 6-hour periods. While peaks at  $\geq$ 24 hours were dominant components in healthy subjects, peak at 8 hours was dominant component in diabetic subjects. ISFG in healthy subjects showed fractal-noise-like moderately correlated dynamics for the time scales from 2 to >12 hours, but the dynamics for >12 hours in diabetic subjects was White-noise-like random sequence, suggesting that glucose regulations in diabetes may be impaired (not regulated) in the time scales of around one day or longer. Although this is a pilot study of a limited sample size, this study suggests that the long-term continuous monitoring of ISFG reveal the dynamics of glucose regulations and their pathophysiology that have not been known from discontinuous or shorter observations of glucose level.

# **Conflict of Interest**

The authors declare no conflict of interest.

# **Author Contributions**

JH analyzed the data and wrote the paper; AY conceived the study and conducted the research; YY designed the protocol and conducted the experiments; NU provided critical review for the manuscript; EY conceived the study; and all authors had approved the final version.

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