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Observational Study

Characteristics of glucose change in diabetes mellitus generalized through continuous wavelet transform processing: A preliminary study

Yoichi Nakamura, Shinya Furukawa

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Abstract

BACKGROUND

The continuous glucose monitoring (CGM) system has become a popular evaluation tool for glucose fluctuation, providing a detailed description of glucose change patterns. We hypothesized that glucose fluctuations may contain specific information on differences in glucose change between type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), despite similarities in change patterns, because of different etiologies. Unlike Fourier transform, continuous wavelet transform (CWT) is able to simultaneously analyze the time and frequency domains of oscillating data.

AIM

To investigate whether CWT can detect glucose fluctuations in T1DM.

METHODS

The 60-d and 296-d glucose fluctuation data of patients with T1DM ($n = 5$) and T2DM ($n = 25$) were evaluated respectively. Glucose data obtained every 15 min for 356 d were analyzed. Data were assessed by CWT with Morlet form ($n = 7$) as the mother wavelet. This methodology was employed to search for limited frequency glucose fluctuation in the daily glucose change. The frequency and enclosed area (0.02625 scalogram value) of 18 emerged signals were compared. The specificity for T1DM was evaluated through multiple regression analysis using items that demonstrated significant differences between them as explanatory variables.

RESULTS

The high frequency at midnight (median: 75 Hz, cycle time: 19 min) and middle frequency at noon (median: 45.5 Hz, cycle time: 32 min) were higher in T1DM *vs* T2DM (median: 73 and 44 Hz; $P = 0.006$ and 0.005 , respectively). The area of the > 100 Hz zone at midnight to forenoon was more frequent and larger in T1DM *vs* T2DM. In a day, the lower frequency zone (15-35 Hz) was more frequent and the area was larger in T2DM than in T1DM. The three-dimensional scatter diagrams, which consist of the time of day, frequency, and area of each signal after CWT, revealed that high frequency signals belonging to T1DM at midnight had a loose distribution of wave cycles that were 17-24 min. Multivariate analysis revealed that the high frequency signal at midnight could characterize T1DM (odds ratio: 1.33, 95% confidence interval: 1.08-1.62; $P = 0.006$).

CONCLUSION

CWT might be a novel tool for differentiate glucose fluctuation of each type of diabetes mellitus using CGM data.

Key Words: Continuous glucose monitoring; Pathophysiology; Fourier, Pseudo-frequency; Contour map; Scalogram matrix

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Core Tip: In the present study, we hypothesized that continuous wavelet transform differentiates glucose fluctuation according to the type of diabetes mellitus. Type 1 diabetes mellitus (T1DM) was characterized by a rapid change (cycle of a 17-24-min interval at midnight). T2DM was characterized by a broad wave (cycle of a 41-96-min interval during a day). Plotting at the three-dimensional scattergram consisting of time, frequency, and an enclosed area of interest revealed that the data of T1DM on the high frequency zone (60-85 Hz) at midnight dispersed into the allocated box, although the glucose fluctuation of T2DM was aligned regularly.

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INTRODUCTION

The levels of blood glucose change during a day because they are controlled by several factors (*e.g.*, a hormonal network, dietary habits, glucose intake, exercise). With the development of continuous glucose monitoring (CGM) systems[1], such changes can be easily and continuously detected in clinical settings[2]. They are occasionally constituted from various waves with complex forms. Therefore, the properties of those waves are able to decompose any signals following elementary functions that are well concentrated in time and frequency.

Recently, the continuous wavelet transform (CWT) method was utilized for the analysis of oscillating data obtained from clinical diagnostic tools, such as those produced by electroencephalography[3,4], electromyography[5,6], electroretinography[7], phonocardiography[8,9], ultrasound sonoelastography[10], and electrocardiography including a longitudinal wave[5,11-14]. This type of processing has epochal merit for simultaneously exploring the time and frequency domains, although Fourier transform is unable to analyze a time domain[15-17].

When considering the pathophysiology of representative abnormal glucose dynamics, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) exhibit marked differences. T1DM is an autoimmune disease characterized by β -cell destruction. T2DM is a complex metabolic disorder, in which the pathophysiology involves an interaction between genetic predisposition and environmental triggers. Based on this knowledge, it was hypothesized that daily glycemic variation may provide insight into the different fluctuation patterns of blood glucose according to the etiologies. Therefore, this study evaluated whether CWT could differentiate signals in blood glucose fluctuation between the two DM groups using CGM data.

MATERIALS AND METHODS

Study population

Data were obtained from consecutive 5 outpatients with T1DM and 25 outpatients with T2DM, who visited the Specified Clinic of Soyokaze CardioVascular Medicine and Diabetes Care (Matsuyama, Ehime, Japan) from December 1, 2017 to June 30, 2018. In the present study, the inclusion criteria were: Patients receiving any diabetic therapy; and age > 20 years. The exclusion criteria were: Presence of a malignancy and history of treatment in the previous 5 years; liver dysfunction with transaminase levels > 100 IU/L; renal dysfunction with estimated glomerular filtration rate < 30 mL/min; implantation of a pacemaker; occurrence of acute coronary syndrome in the previous 2 mo; and pregnancy.

Furthermore, 8 outpatients treated for hypertension or dyslipidemia with normal glucose fluctuation applied through an in-hospital communication sheet supplied by the clinical study team. In addition to those volunteers, two healthy volunteers who applied *via* an invitation on the website homepage of the clinic were also included. Their data were utilized in this study as a reference to determine the normal glucose levels through CWT processing. All subjects provided written informed consent for their participation in this study. This study was approved by the ethics committee of Ehime University (approval No. 1711001).

Data collection and statistical calculation of glucose variance

A sensor of the flash glucose monitoring system (FreeStyle Libre Pro®; Abbott, Chicago, IL, United States) was attached to the back of the upper arm of all subjects. The memorized text document data obtained from subcutaneous tissue every 15 min over a period of 14 d were converted to comma-separated values files. These data were transformed through CWT processing. The 60-d data of 5 patients with T1DM and 296-d data obtained from 25 patients with T2DM were evaluated. Glucose data of a total of 356 d were employed in this analysis, because this evaluation tool was used to search for a limited frequency glucose fluctuation into the daily glucose change.

CWT

Wavelet transform decomposes a signal into a series of dilated and translated versions of the mother wavelet function [17]. The form of the CWT of a signal is defined by the following formula.

$$c_{a,b} = \int_{\mathbb{R}} x(t) \frac{1}{\sqrt{a}} \psi * \left(\frac{t-b}{a} \right) dt$$

$$\psi(x) = \pi^{-1/4} \cos(7x) e^{-x^2/2}$$

In this study, $\psi(x)$ was nominated as a Morlet form, using wave number 7 as the mother wavelet. This process was performed using OriginPro® version 2018 (OriginLab Co., Northampton, MA, United States). This function computes the real continuous wavelet coefficient of $x(t)$ for each given scale presented in the scale vector a and each position b from 1 to 96 during 24 h. The obtained scalogram matrix by CWT was presented in the form of a contour diagram. In case of data loss due to a sensor error, the data of that day were excluded from the analysis. Consequently, this application assigned a pseudo-frequency with a cycle of 1 Hz wave over a 24-h period. The signals that emerged on the contour diagram were divided into 18 areas according to the time and frequency zone, which corresponded to the peak scalogram value. The frequency zone was defined as follows: 60-85 Hz, high frequency signal (P1-P3); 35-55 Hz, middle frequency signal (P4-P8); > 100 Hz, super-high frequency signal (P9-P11); and 15-35 Hz, lower frequency signal (P12-P18). If the enclosed area at the 0.02625 scalogram value fused to another area of different points, those signal data were adopted at the point that showed the highest scalogram value. The other area points, which had a lower scalogram value, defined defect data because those borderlines could not be fixed.

Signal characteristics of T1DM

The frequency at a point that showed the peak scalogram value was compared between the groups to clarify the specific glucose fluctuation in T1DM. The area enclosed at the scalogram value of 0.02625 on the contour diagram was also evaluated. Subsequently, the relationships of factors exhibiting significant differences with the specific glucose fluctuation in T1DM were determined through multivariate analysis.

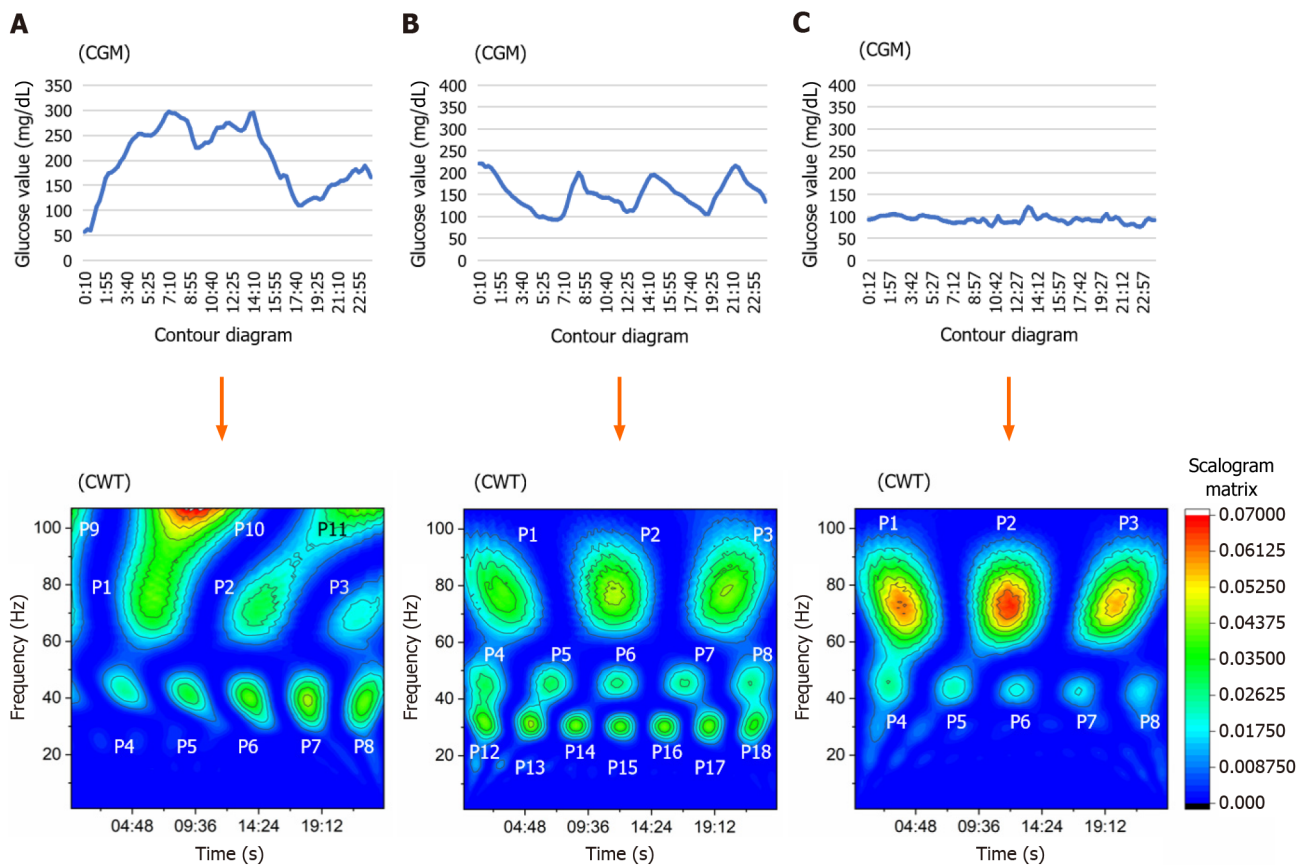
Statistical analysis

The statistical methods used in this study were reviewed by Data Seed Inc., a consulting company specializing in biostatistics (<https://dt-seed.com>, info@dt-seed.com). Age, body mass index, hemoglobin A1c levels, and daily dose of insulin used were compared between the T1DM and T2DM groups using the Mann-Whitney U test. All frequencies and areas, which emerged through CWT in the two groups, were also evaluated using the Mann-Whitney U test. The statistically calculated data of mean glucose and mean amplitude of glucose excursion (MAGE) were converted to natural logarithm, because they were obtained based on an approximate normal distribution. Because of a normal distribution, those indices together with log mean glucose, standard deviation, percent coefficient of variation, and log MAGE were evaluated using the unpaired t -test. Sex, medications, and number of signals obtained through CWT were assessed using the Fisher's exact test. For the selection of possible factor characterized in T1DM glucose fluctuation, logistic regression analysis was employed using factors that showed significant differences between the two groups as explanatory variables. $P < 0.05$ was considered statistically significant.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to include additional statistical functions frequently used in biostatistics [18].

RESULTS

The characteristics of subjects and medications used in both diabetes groups, as well as data of subjects without diabetes (reference), are summarized in Table 1. The average data for glucose change did not show a significant difference between the groups. However, significant differences between the two groups were recorded for the standard deviation, percent coefficient of variation, and log MAGE. The representative contour diagram that emerged from glucose



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Figure 1 Representative image of the contour diagram converted through continuous wavelet transform of continuous glucose monitoring data associated with both diabetes groups, including a subject without diabetes. The upper panels indicate the continuous glucose monitoring data of each group. The bottom panels indicate the contour diagram after continuous wavelet transform (CWT) processing. The CWT produced 18 signals from the continuous glucose shift. The signals were divided according to the time and frequency zone, which corresponded to the peak scalogram value. P1-P3, P4-P8, P9-P11, and P12-P18 belonged to a high frequency zone (about 60-85 Hz; indicating a wave period of 17-24 min), middle frequency zone (35-55 Hz; indicating a wave period of 26-41 min), super-high frequency zone (> 100 Hz; indicating a wave period < 14 min), and low frequency zone (15-35 Hz; indicating a wave period 41-96 min), respectively. A: Type 1 diabetes mellitus; B: Type 2 diabetes mellitus; C: A subject without diabetes as a reference. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; CGM: Continuous glucose monitoring; CWT: Continuous wavelet transform.

fluctuation after conversion through CWT is shown in [Figure 1](#). The T1DM group showed some signals on the super-high frequency zone (rate: 20% at P9, 27% at P10) in contrast with the T2DM group (rate: 7% at P9, 11% at P10) ($P = 0.003$ and $P = 0.003$, respectively). Signals of the T2DM group appeared more frequently on the lower frequency zone (*i.e.*, 15-35 Hz) on the contour map, indicating a time cycle of 41-96 min) throughout the day ([Table 2](#)). The median frequency of P1 signal in the T1DM group was 75 Hz (quartile: 72-78 Hz), indicating a time cycle of 19 min. This value was higher than that noted in the T2DM group [median: 73 Hz (quartile: 71-75 Hz)] ($P = 0.006$). The wave period of this range signals in T1DM was 18-20 min. Moreover, the median frequency of P6 signal in the T1DM group was 45.5 Hz (quartile: 44-46.25 Hz), indicating a time cycle of 32 min. Signals that emerged on the middle frequency range around noon each day were higher than those observed in the T2DM group [median: 44 Hz (quartile: 42-45 Hz)] ($P = 0.005$) ([Table 3](#)). The area of P9 and P10 points of the T1DM group was larger than that of the T2DM group, although both groups exhibited less emergence in that frequency zone compared with other zones. The area of the lower frequency zone, which was positioned at P12-P17, was smaller and less frequent in the T1DM group *vs* the T2DM group ([Table 4](#)).

The three-dimensional (3D) scatter diagrams, which consist of a time of a day, a frequency, and an area of each signal after CWT, are demonstrated in [Figure 2](#). Subjects without diabetes showed three high frequency signals (P1-P3) and five middle frequency signals (P4-P8) regularly distributed in a similar interval during 24 h. Occasionally, some cases exhibited signals in the low frequency zone. The distribution of T2DM was similar to that observed in subjects without diabetes, although each signal zone expanded toward a time (x-axis) and an area (y-axis) direction; the frequency fluctuation (z-axis) was small for all signals. Furthermore, signals that emerged on the low frequency zone were increased, whereas other signals of the super-high frequency zone were observed in the glucose fluctuation of patients with T2DM in a few days. By contrast, the 3D scatter diagram of T1DM showed a destroyed distribution pattern, particularly in the frequency width of the P1 signal. Consequently, the borderline of each signal disappeared, complicating the differentiation of signals.

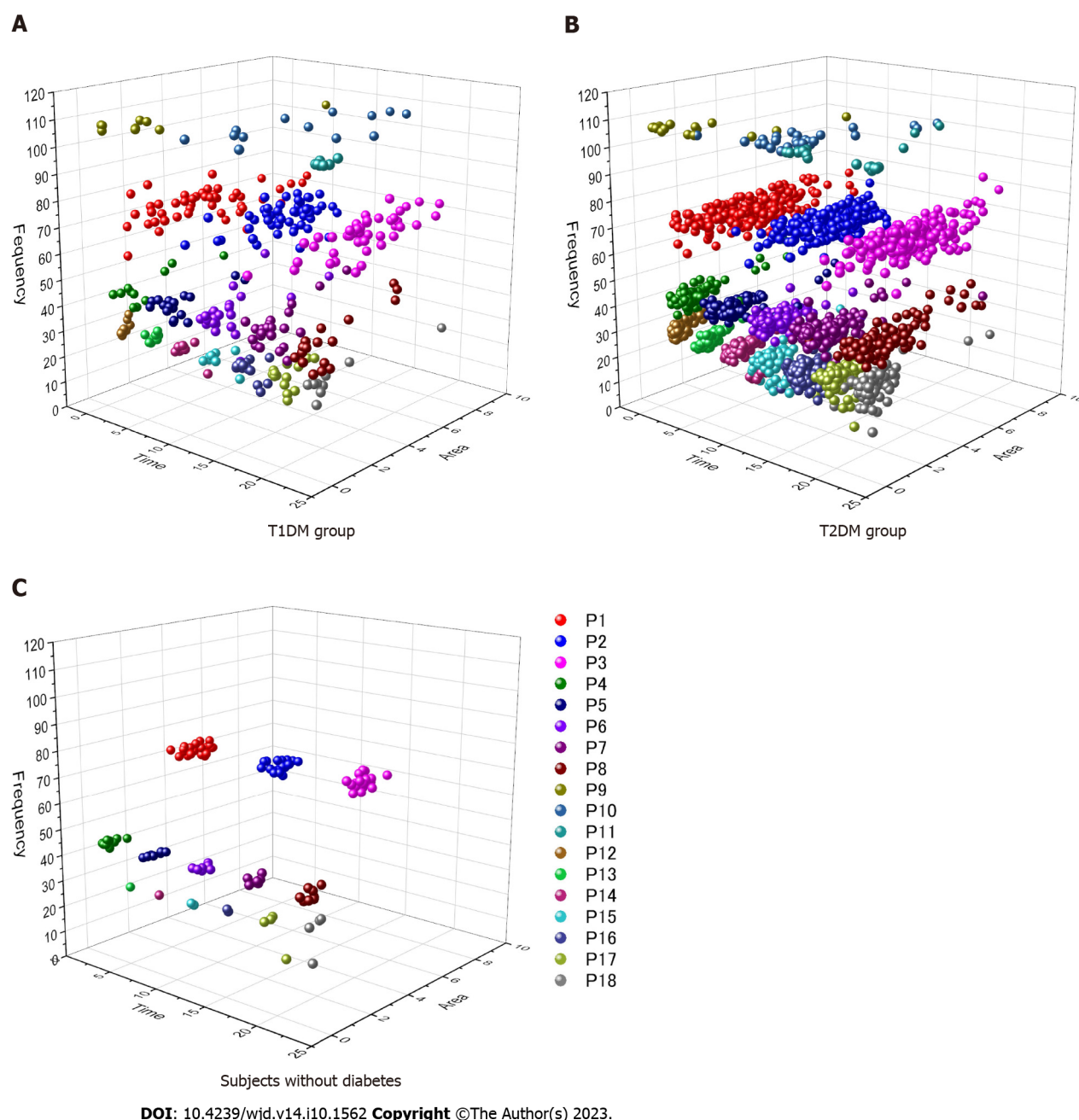


Figure 2 Comparison of the three-dimensional scattering diagram between groups. The x-axis indicates time during a day; the y-axis indicates the area enclosed at the 0.02625 scalogram value; the z-axis indicates a pseudo-frequency determined after continuous wavelet transform processing. The wave cycles of P1 signals belonging to type 1 diabetes mellitus (T1DM) were distributed during 17–24 min. The loose distribution of P1 signal wave length characterized T1DM. A: Type 1 diabetes mellitus group; B: Type 2 diabetes mellitus group; C: Subjects without diabetes.

In the multivariate analysis, the area data of P13, P14, and P15 were removed because the value of the variance inflation factor was > 5 . Furthermore, the area data of P9, P12, and P16 were also removed because those items had a large 95% confidence interval (CI) (1.33×10^{-16} to 1.90×10^{12} at P9, 0.08–50.4 at P12, and 0.01–213 at P16) (Supplementary Table 1). Consequently, the frequency of P1 and P6 signals and the area of P10 and P17 signals were nominated as explanatory variables. Logistic regression analysis revealed that the frequency of the P1 signal could characterize the specific T1DM distribution [odds ratio (OR) = 1.33, 95%CI: 1.08–1.62; $P = 0.006$] (Table 5). In both analyses with or without a large CI at P9, P12, and P16, those results indicated the frequency of P1-characterized T1DM glucose fluctuation.

DISCUSSION

The present evaluation of 356-d glucose data demonstrated that CWT processing can detect the specific glucose wave form of T1DM with regard to the onset time and time cycle in the contour map. It revealed that the P1 signal wave length was broadly distributed during a 17–24 min interval at midnight. This finding indicated that the cycle of glucose change

Table 1 Background characteristics of patients with diabetes (*n* = 30) and subjects without diabetes (*n* = 10)

Characteristic	T1DM group	T2DM group	<i>P</i> value	Subjects without diabetes
Days evaluated, <i>n</i>	60	296	-	23
Age, yr	50 (43-66)	61 (48-71)	0.419 ^a	60 (47.5-72.3)
Sex as female/male, <i>n</i>	2/3	7/18	0.622 ^b	4/6
BMI in kg/m ²	28.3 (26.0-39.3)	26.0 (22.5-28.6)	0.229 ^a	22.9 (21.7-27.2)
HbA1c, %	8.8 (8.6-9.3)	7.6 (6.9-9.0)	0.220 ^a	5.4 (5.4-5.5)
Log MG	5.09 ± 0.32	5.11 ± 0.30	0.579 ^c	4.61 ± 0.08
SD	56.26 ± 18.63	44.60 ± 20.29	< 0.001 ^c	11.58 ± 2.37
%CV	34.85 ± 11.85	25.53 ± 7.43	< 0.001 ^c	11.56 ± 2.66
Log MAGE	4.58 ± 0.40	4.41 ± 0.42	0.003 ^c	3.17 ± 0.27
Medication, <i>n</i>				
Metformin	0	5	0.556 ^b	N/A
DPP-4 inhibitor	0	21	0.001 ^b	N/A
α-GI	0	3	1.000 ^b	N/A
Thiazoline	0	14	0.045 ^b	N/A
SGLT2 inhibitor	0	4	1.000 ^b	N/A
SU	0	0	1.000 ^b	N/A
GLP-1 RA	0	5	0.556 ^b	N/A
Insulin	5	16	0.286 ^b	N/A
Total insulin dose in U	37 (34-38)	8 (0-20)	0.008 ^a	N/A
Ultra-rapid in U	21 (18-26)	0 (0-11)	0.030 ^a	N/A
Lasting in U	16 (11-20)	2 (0-14)	0.022 ^a	N/A

^aMann-Whitney *U* test.^bFisher's exact test.^cUnpaired *t*-test.

BMI: Body mass index; CV: Coefficient of variation; DPP-4: Dipeptidyl peptidase 4; GI: Glucosidase inhibitor; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; HbA1c: Hemoglobin A1c; MAGE: Mean amplitude of glucose excursion; MG: Mean glucose; N/A: Not applicable; SD: Standard deviation; SGLT2: Sodium-glucose co-transporter type 2; SU: Sulfonylurea; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

in T1DM was irregular and involved different waves around a 19 min interval at midnight. On the other hand, T2DM was characterized by low frequency signals distributed during a 39-85 min cycle that emerged frequently, and those areas increased during 1 d.

The CWT represents the time-frequency space of a signal as a matrix with magnitude values that can be readily visualized in the form of a heat map to reveal important features, transient effects, and anomalies[17]. T1DM showed super-high frequency signals from midnight to forenoon with high probability. Furthermore, the distribution of P1 signals in the T1DM group showed differences in time, area, and frequency on the contour map after CWT processing. However, the distribution in the T2DM group was similar to that observed in subjects without diabetes. This observation suggested that T1DM exhibits complex and short glucose changes. Those rapid and varied glucose changes at midnight might reflect the presence of the dawn phenomenon or Somogyi effect. Notably, a regular signal appearance observed after CWT may indicate preserved basal insulin secretion. By contrast, increased signals on the low frequency zone were frequently noted in the T2DM group. This finding suggested that slow glucose change components were included in the CGM glucose data. However, the reason underlying this finding could not be determined in this study. It is hypothesized that the results might reflect the effects of medications or the pathophysiology of insulin resistance.

Glucose variability in T1DM is largely due to the lack of or diminished insulin secretion. The frequency of fluctuation might be an important phenomenon when considering differences in the pathophysiology of diabetes. Previous studies have reported increases in several statistical calculation markers of T1DM such as the standard deviation of blood glucose change, percent cyclic variation, and MAGE[19,20]. Those indices are calculated based on the amplitude of the glucose value. However, CWT processing discovered the object wave of interest from daily glucose change; furthermore, this method could detect the time when the target wave presented during a day. This is fundamentally different from conventional statistical indices. Unfortunately, CWT could not reverse original data; therefore, it could not detect the amplitude width of the glucose wave, although the value of the scalogram could detect the wave power.

Table 2 Prevalence rate of emerging items on the contour map treated by a continuous wavelet transform between the type 1 diabetes mellitus and type 2 diabetes mellitus groups, *n* = 356

Time zone	Position	Frequency zone	Prevalence rate, %		
			T1DM group	T2DM group	<i>P</i> value
Midnight	P9	Super-high	20	7	0.003
	P1	High	85	88	0.527
	P4	Middle	20	34	0.047
	P12	Low	13	26	0.032
	P13	Low	15	32	0.008
Daytime	P10	Super-high	27	11	0.003
	P2	High	88	93	0.299
	P5	Middle	32	39	0.311
	P6	Middle	40	43	0.670
	P7	Middle	42	48	0.478
	P14	Low	15	33	0.005
	P15	Low	15	35	0.001
Night	P11	Super-high	13	10	0.491
	P3	High	83	94	0.014
	P8	Middle	42	50	0.321
	P17	Low	25	43	0.014
	P18	Low	22	41	0.005

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Recently, it was reported that the use of artificial intelligence and CWT may improve the accuracy of atrial fibrillation detection through electrocardiography (10 s)[14]. This proposed evaluation method based on CGM data may be able to accurately and promptly diagnose pathogenesis through the use of deep learning after CWT processing.

Limitation

In the present study, it was not possible to remove the effects of medications on glucose fluctuation owing to the small sample size. To exclude such bias and identify the specificity for T1DM glucose fluctuation, a large number of patients are required because the degree of impaired β cells differs depending on the stage. Furthermore, T2DM had a different pathophysiology, such as an insulin resistance or a decrease of insulin secretion. Glucose fluctuations differ between days. Therefore, when the pathophysiology of diabetes is assessed, it is important to determine whether glucose data from several days were averaged or data from a single day were used. In this study, the latter approach was employed. Furthermore, this analysis could not determine the amplitude of the target wave form, although the duration of a wave period was obtained because CWT could not reverse original data after processing.

CONCLUSION

The contour diagram obtained through CWT demonstrated that fluctuation in the high frequency wave, indicating a time cycle of 17-24 min at midnight, could characterize T1DM based on glucose transition. The scatter diagram of signals demonstrated that the distribution pattern in T1DM was destroyed, although T2DM exhibited a similar pattern to that observed in subjects without diabetes. The present method may contribute to the differentiation of glucose fluctuations according to the etiology of DM.

Table 3 Comparison of frequency on the contour map treated by a continuous wavelet transform between the type 1 diabetes mellitus and type 2 diabetes mellitus groups, $n = 356$

Time zone	Position	Frequency zone	T1DM group			T2DM group			P value
			Min	Median	Max	Min	Median	Max	
Midnight									
	P9	Super-high	106	108	108	106	107	108	0.433
	P1	High	61	75	85	61	73	80	0.006
	P4	Middle	39	45	53	38	45	56	0.265
	P12	Low	29	30.5	38	28	32	36	0.634
	P13	Low	29	30	36	27	31	35	0.965
Daytime									
	P10	Super-high	106	108	108	106	107	108	0.100
	P2	High	66	75	84	59	74	81	0.088
	P5	Middle	37	45	50	37	44	51	0.418
	P6	Middle	33	45.5	58	37	44	51	0.005
	P7	Middle	35	45	54	33	44	57	0.225
	P14	Low	25	30	33	18	30	35	0.895
	P15	Low	25	30	32	17	30	37	0.885
	P16	Low	25	30.5	33	20	30	36	0.725
Night									
	P11	Super-high	107	108	108	105	107	108	0.004
	P3	High	65	75	85	59	74	86	0.104
	P8	Middle	36	45	54	37	44	53	0.893
	P17	Low	25	28.5	33	17	29	36	0.395
	P18	Low	26	33	35	17	31	37	0.166

Max: Maximum; Min: Minimum; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 4 Comparison of area on the contour map treated by a continuous wavelet transform between the type 1 diabetes mellitus and type 2 diabetes mellitus groups, $n = 356$

Time zone	Position	Frequency zone	T1DM group			T2DM group			P value
			Min	Median	Max	Min	Median	Max	
Midnight									
	P9	Super-high	0.00	0.00	8.70	0.00	0.00	5.34	0.008
	P1	High	0.00	3.01	8.99	0.00	2.75	8.14	0.866
	P4	Middle	0.00	0.00	5.06	0.00	0.00	5.67	0.111
	P12	Low	0.00	0.00	0.60	0.00	0.00	4.01	0.043
	P13	Low	0.00	0.00	0.65	0.00	0.00	1.83	0.011
Daytime									
	P10	Super-high	0.00	0.00	8.32	0.00	0.00	6.81	0.001
	P2	High	0.00	3.96	5.87	0.00	3.65	6.43	0.267
	P5	Middle	0.00	0.00	3.32	0.00	0.00	5.23	0.249
	P6	Middle	0.00	0.00	5.77	0.00	0.00	3.70	0.812

Night	P7	Middle	0.00	0.00	5.29	0.00	0.00	5.50	0.348
	P14	Low	0.00	0.00	0.95	0.00	0.00	3.91	0.005
	P15	Low	0.00	0.00	1.42	0.00	0.00	4.40	0.003
	P16	Low	0.00	0.00	1.63	0.00	0.00	2.22	0.020
	P11	Super-high	0.00	0.00	1.07	0.00	0.00	6.48	0.257
	P3	High	0.00	3.39	8.38	0.00	3.75	9.18	0.258
	P8	Middle	0.00	0.00	5.09	0.00	0.00	6.70	0.163
	P17	Low	0.00	0.00	2.02	0.00	0.00	2.47	0.031
	P18	Low	0.00	0.00	7.09	0.00	0.00	7.08	0.059

Max: Maximum; Min: Minimum; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 5 Logistic regression analysis for the identification of characteristics of type 1 diabetes mellitus with selected factors, $n = 356$

Selected item	Odds ratio	95%CI		P value
		Lower	Upper	
Frequency of P1 signal	1.33	1.08	1.62	0.006
Frequency of P6 signal	0.84	0.63	1.12	0.232
Area of P10 signal	1.24	0.72	2.14	0.432
Area of P17 signal	1.24	0.29	5.29	0.771

CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Recently, the continuous glucose monitoring (CGM) system was readily accepted in the clinical setting. Although that system provides details of the glucose fluctuation that occur during a day, occasionally, a lot of vague data might confuse the interpretation of a glucose shift. Continuous wavelet transform (CWT) is a novel approach for analyzing oscillating data in the case of clinical field. That methodology is able to analyze time domain and frequency domain simultaneously, although Fourier transforms are limited to the analysis of frequency domain.

Research motivation

When the glucose change during a day can replace a waveform, the glucose fluctuation includes some waveform in the glucose change. We hypothesized the specific waveform of type 1 diabetes mellitus (T1DM) might be present because glucose change pattern might be different from T2DM due to a different etiology. The CWT is an available method to explore the target substance into the objects through analyzing oscillating data.

Research objectives

The present study evaluated 60-d glucose fluctuation data obtained from T1DM patients ($n = 5$) and 296-d data from T2DM patients ($n = 25$).

Research methods

The data obtained every 15 min from a flash glucose monitoring system during 14 d were converted through the CWT process. In the present study, Morlet form ($n = 7$) was employed as the mother wavelet. The produced scalogram matrix by CWT was converted to the contour diagram. Through this process, the waveform obtained from CGM divided 18 segment signals, that is, 3 super-high frequency (> 100 Hz) zones, 3 high frequency (60-85 Hz) zones, 5 middle frequency (35-55 Hz) zones, and 7 low frequency (15-35 Hz) zones. The frequency and an enclosed area at 0.02625 scalogram value obtained from those emerged signals were compared between the T1DM and T2DM groups at 18 segments. To identify the specificity of T1DM, a statistical approach was applied. The explanatory variables of a logistic regression analysis model were the nominated items, which were significantly different between groups.

Research results

In the T1DM group, super-high frequency signals at midnight and forenoon emerged more frequently. On the other hand, the prevalence rate of low frequency signals in a day in the T2DM group was increased. The high frequency signal at night and middle frequency signal also emerged frequently in the T2DM group. The frequency of the high frequency signal at midnight and the middle frequency signal at noon in the T1DM group were higher than those of the T2DM group. The areas of low frequent zone in a day in the T2DM group were significantly higher than those of the T1DM group. In multivariate analysis, some data were excluded because of the variance inflation factor and a large 95% confidence interval (CI). Finally, the fine waveform presented in the high frequency signal zone at midnight showed the characteristic wave pattern of T1DM (odds ratio = 1.33, 95%CI: 1.08-1.62; $P = 0.006$).

Research conclusions

Through the contour diagram after CWT processing, the fine waveform indicating a time cycle of 17-24 min at midnight had characterized the glucose fluctuation of T1DM. However, the low frequency signals emerged frequently in T2DM in 1 d.

Research perspectives

Confirming the accuracy of present study required a lot of data to be obtained from both groups. If an artificial intelligence including deep learning is available in this analyzing system, it will obtain the results rapidly and correctly because this manual process takes a lot of time, even though it is a 1 d data calculation. Furthermore, this novel approach will be available to research the relationship between the diabetic complications and any specific waveform and might select medications according to the patients' conditions to decrease any diabetic complications.

FOOTNOTES

Author contributions: Nakamura Y was the guarantor, designed the study, performed the acquisition, analysis and interpretation of the data, and drafted the manuscript; Furukawa S participated in the study design, data interpretation, and manuscript drafting.

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