Decreased complexity of glucose dynamics in diabetes: evidence from multiscale entropy analysis of continuous glucose monitoring system data

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Chen J-L, Chen P-F, Wang H-M. Decreased complexity of glucose dynamics in diabetes: evidence from multiscale entropy analysis of continuous glucose monitoring system data. Am J Physiol Regul Integr Comp Physiol 307: R179–R183, 2014. First published May 7, 2014; doi:10.1152/ajpregu.00108.2014.—Parameters of glucose dynamics recorded by the continuous glucose monitoring system (CGMS) could help in the control of glycemic fluctuations, which is important in diabetes management. Multiscale entropy (MSE) analysis has recently been developed to measure the complexity of physical and physiological time sequences. A reduced MSE complexity index indicates the increased repetition patterns of the time sequence, and, thus, a decreased complexity in this system. No study has investigated the MSE analysis of glucose dynamics in diabetes. This study was designed to compare the complexity of glucose dynamics between the diabetic patients (n = 17) and the control subjects (n = 13), who were matched for sex, age, and body mass index via MSE analysis using the CGMS data. Compared with the control subjects, the diabetic patients revealed a significant increase (P < 0.001) in the mean (diabetic patients 166.0 ± 10.4 vs. control subjects 93.3 ± 1.5 mg/dl), the standard deviation (51.7 ± 4.3 vs. 11.1 ± 0.5 mg/dl), and the mean amplitude of glycemic excursions (127.0 ± 9.2 vs. 27.7 ± 1.3 mg/dl) of the glucose levels; and a significant decrease (P < 0.001) in the MSE complexity index (5.09 ± 0.23 vs. 7.38 ± 0.28). In conclusion, the complexity of glucose dynamics is decreased in diabetes. This finding implies the reactivity of glucoregulation is impaired in the diabetic patients. Such impairment presenting as an increased regularity of glycemic fluctuating pattern could be detected by MSE analysis. Thus, the MSE complexity index could potentially be used as a biomarker in the monitoring of diabetes.

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**METHODS**

**Subjects.** A group of 17 patients with diabetes from the outpatient clinic of a teaching hospital and a group of 13 control subjects were recruited for this study. The characteristics of these subjects are shown in Table 1. The diabetes group included both Type 1 and Type 2 diabetes. The diabetes and control groups were matched for sex, age, height, weight, and body mass index (Table 1). Diabetic patients were treated with insulin in nine patients and with oral hypoglycemic agents: sulfonylurea in five patients, biguanide in seven patients, and dipeptidyl peptidase-4 inhibitor in five patients. Participants were instructed to eat as their usual content and amount during meals, to avoid eating big meals, to eat meals at typical times, and to avoid rigorous physical activity during the monitoring period. The study protocol was approved by the local ethics committee, and all participants gave their informed consent. The study was conducted according to the principles of the Helsinki declaration.

**Measurement of interstitial glucose levels.** Subcutaneous interstitial fluid glucose levels were checked every 5 min for 72 h using a continuous glucose monitoring system (CGMS, Medtronic MiniMed, Northridge, CA, USA). The CGMS recorded a total of 288 interstitial glucose level data points ranging from 40 to 400 mg/dl over a 24-h period. With CGMS, the participants are required to self-monitor finger-stick blood glucose by a glucose meter at least four times a day for calibration. After recording, the data in CGMS were downloaded to a personal computer and further extracted to get a glucose sequence for each participant.

**Linear analysis.** The mean and the standard deviation of the glucose levels were computed for each glucose sequence. The MAGE were calculated by measuring the arithmetic mean of the differences between levels were computed for each glucose sequence. The MAGE were calculated by

\[
\text{MAGE} = \frac{1}{N} \sum_{i=1}^{N} (x(i) - \bar{x})
\]

where \(x(i)\) is the glucose level at time \(i\), \(\bar{x}\) is the mean glucose level, and \(N\) is the number of data points in the sequence. The MAGE of the glucose levels in both the control subjects and the diabetic patients are shown in Table 2. Additionally, the standard deviation, or the MAGE of the glucose levels in both the control subjects and the diabetic patients are shown in Table 2. Furthermore, the standard deviation was included for MAGE calculation. We calculated standard deviation was included for MAGE calculation. We calculated

\[
\text{Standard deviation} = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (x(i) - \bar{x})^2}
\]

Second, we computed sample entropy for each coarse-grained sequence. Sample entropy is the negative natural logarithm of conditional probability that two similar sequences of length \(m\) remain similar (within a tolerance level, \(r\)) when the sequence length increases to \(m + 1\), where self-matches are not included in calculating the probability (29). We used \(m = 2\) and \(r = 0.15\) of the standard deviation of the original sequence for sample entropy computation, and we set the largest scale factor \(M = 7\) (29). Sample entropy quantifies the degree of irregularity and unpredictability of an ordered sequence. Greater entropy denotes fewer repetitions of the same pattern in the sequence and thus reflects greater irregularity.

Third, we plotted each calculated sample entropy with respect to the corresponding scale factor and got an MSE plot. Next, the MSE complexity index was defined and calculated by the area under the MSE plot, from \(\tau = 1\) to \(\tau = M\) (6). As such, a sequence with greater irregularity over multiple temporal scales has more area under the MSE curve and thus exhibits higher complexity.

**Statistical analysis.** The Mann-Whitney U-test was used for comparisons of glucose dynamics parameters between the diabetic patients and the control subjects. Correlations were computed by Spearman’s correlation coefficient. Statistical significance was assumed for \(P < 0.05\). Data were expressed as means ± SE. Data were analyzed using SPSS for Windows (SPSS, Chicago, IL).

**RESULTS**

Figure 1 shows the 72-h glucose profile and the MSE plots in a control subject and in a diabetic patient. A larger glucose fluctuation profile was evident in the diabetic patient compared with the control subject. The MSE plot was constructed by calculating sample entropy with respect to each scale factor. For each scale factor, the calculated sample entropy of the diabetic patient was lower than that of the control subject.

The diabetic patients revealed a significant increase \((P < 0.001)\) in the mean, the standard deviation, and the MAGE of the glucose levels (Table 2). In addition, the MSE complexity index in the diabetic patients was significantly lower than that in the control subjects (diabetic patients 5.09 ± 0.23 vs. control subjects 7.38 ± 0.28, \(P < 0.001, \text{Table 2} \)).

Figure 2 presents the average MSE plots of the control subjects and the diabetic patients. The average MSE plots were constructed by averaging sample entropy with respect to each scale factor in the diabetes and the control groups, respectively. For scale factor 1 to 7, the mean of the sample entropy with respect to each scale factor in the diabetic patients was significantly lower than that in the control subjects (Fig. 2 and Table 2). For correlation analysis, we found that the MSE complexity index was not statistically correlated with the mean, the standard deviation, or the MAGE of the glucose levels in both the control subjects and the diabetic patients. However, there was significant correlation \((P < 0.001)\) between the standard deviation and the MAGE of the glucose levels in both the control subjects \((r = 0.885)\) and the diabetic patients \((r = 0.926)\).

**DISCUSSION**

Our results indicate that the MSE complexity index \((\text{the sum of sample entropy calculated over multiple scales})\) was reduced in the diabetic patients compared with that in the control subjects. This suggests that the complexity of glucose dynamics is decreased in diabetes.

Traditionally, frequent blood glucose sampling by glucose meters and HbA1c are used to monitor the blood glucose profile in the patients with diabetes. However, important glucose
changes could be missed by the limited blood glucose sampling number. The HbA1c denotes the mean blood glucose level over an approximate 3-mo period and cannot fully reflect the fluctuations of blood glucose that is an important factor in the monitoring and management of diabetes. With CGMS, it is feasible to detect the subtle changes of interstitial fluid glucose levels, which reflect blood glucose levels (13). Parameters used to quantify the glucose data collected by CGMS include mean glucose level, standard deviation, and range. These parameters derived from the linear analytic methods are useful in clinical practice. However, the blood glucose homeostasis system is regulated by multiple nonlinearly mutually interacting systems over multiple time scales in a complex way. It would be more appropriate to use the method of complexity analysis in analyzing the CGMS data, and this could bring new insight into the regulating mechanism of the blood glucose system.

The human physiological systems, as well as those of many other living organisms, are regulated by many mutually interacting controlling mechanisms. These physiological systems are complex with unpredictability in nature, yet they are not completely regular, nor do they exhibit total randomness. By the complexity theory (27), a healthy physiological system

| Table 2. Parameters of glucose dynamics in the control subjects and diabetic patients |
|----------------------------------|------------------|------------------|---|
|                                  | Control Subjects | Diabetic Patients | P value |
| Mean, mg/dl                     | 93.3 ± 1.5       | 166.0 ± 10.4     | < 0.001 |
| SD, mg/dl                       | 11.1 ± 0.5       | 51.7 ± 4.3       | < 0.001 |
| MAGE, mg/dl                     | 27.7 ± 1.3       | 127.0 ± 9.2      | < 0.001 |
| CI                              | 7.38 ± 0.28      | 5.09 ± 0.23      | < 0.001 |
| SE1                             | 0.51 ± 0.04      | 0.37 ± 0.02      | 0.008  |
| SE2                             | 0.72 ± 0.04      | 0.53 ± 0.02      | 0.001  |
| SE3                             | 0.95 ± 0.04      | 0.65 ± 0.03      | < 0.001 |
| SE4                             | 1.13 ± 0.04      | 0.75 ± 0.03      | < 0.001 |
| SE5                             | 1.25 ± 0.05      | 0.84 ± 0.04      | < 0.001 |
| SE6                             | 1.34 ± 0.05      | 0.93 ± 0.04      | < 0.001 |
| SE7                             | 1.45 ± 0.05      | 0.99 ± 0.04      | < 0.001 |

Data are expressed as means ± SE. Mean, mean glucose level; SD, standard deviation of glucose level; MAGE, mean amplitude of glycemic excursions; CI, multiscale entropy complexity index; SE1-7, sample entropy calculated at scale factor 1–7. Differences between means were assessed by Mann-Whitney U-test.

Fig. 1. The 72-h glucose profile (top) and the multiscale entropy plots (bottom) in a control subject (left) and in a diabetic patient (right).

Fig. 2. Average multiscale entropy plots of the control subjects (n = 13) and the diabetic patients (n = 17). Symbols (● for the control subjects and △ for the diabetic patients) represent the means of sample entropy with respect to scale factor in each group. Bars represent the SE.
would have a more complex structure in its physiological signals. This complex structure could help the system adapt external perturbation and resist stressors. In such a way, the healthy system could finely adjust its reaction to the stimuli and make a relatively stable homeostatic environment in it. In contrast, the aging or pathological system, due to the malfunction of the regulating loop, would assume a decreased complexity in its physiological signals. Thus, their adaptability to the external changes would be compromised. Such impairment in system complexity could be quantified by adequate analytic methods.

The MSE analysis is one of the nonlinear methods proposed to quantify the complexity of a physical or biological complex system. It calculates the sample entropy of a system over several time scales using the coarse graining technique. Applying MSE analysis, decreased complexity of heart rate dynamics has been observed in aging, as well as in patients with heart failure (3), diabetes (12), and major depression (15, 32). It has also been shown that reduction of heart rate complexity calculated by MSE could predict mortality in trauma patients (30) and in congestive heart failure patients (11). In addition, reduced complexity of EEG in Alzheimer’s disease was noted with the MSE analysis (7, 26). Results from these studies invariably revealed that “loss of complexity” for the studied systems is associated with aging or disease.

Using MSE analysis of glucose dynamics, we first showed that the MSE complexity index was reduced in the diabetic patients compared with that in the control subjects. The lower MSE complexity index in the patients with diabetes indicates the increased repetitions of glucose fluctuating pattern, and thus the lower complexity in blood glucose homeostasis system for these patients. The decreased complexity of glucose dynamics in the diabetic patients indicates that the reactivity of glucoregulation is impaired in these patients. Patients with diabetes cannot adequately respond to the changes of blood glucose level induced by perturbation, such as meals and exercise. They are unable to reactively secrete adequate amounts of glucose-related hormones, such as insulin and glucagon, to maintain a relatively stable blood glucose level. Therefore, diabetic patients manifest both a greater fluctuating blood glucose profile (indicated by the increased standard deviation and MAGE of the glucose levels) and an increased regularity of glycemic fluctuating pattern via the decreased MSE complexity index (compared with the control subjects).

Our results revealed reduced MSE complexity index in the patients with diabetes, and this implies the loss of complexity of blood glucose dynamics in these patients. This decreased complexity of glucose dynamics could be attributed to the impaired glucose controllability noted in the patients with diabetes. These results are consistent with previous studies and support the notion that “loss of complexity” is associated with aging and disease. Thus, the parameter derived from MSE analysis of glucose dynamics could be used as a biomarker to distinguish the diabetic patients from the control subjects.

For correlation analysis, we disclosed that there was significant correlation between the standard deviation and the MAGE of the glucose levels in both the control subjects and the diabetic patients. This indicates that the MSE complexity index is a new parameter for analyzing CGMS data. The standard deviation and the MAGE of the blood glucose levels denote the degree of swinging in glycemic amplitude. However, the MSE complexity index reflects the temporal relationships of glycemic patterns within the blood glucose profile. This parameter gives new insight into the understanding of the mechanism for the impaired glucoregulation in diabetes. Future studies could be directed to examine whether the MSE complexity index of blood glucose dynamics could be used as an indicator to evaluate the effects from changes of different modalities (e.g., life style modification and drugs) given to the patients with diabetes.

There are some limitations to the present study. First, in this study, the variations of meals, activities, and medications of the participants were not strictly controlled, and these factors may confound the glycemic profile. Second, we estimated the blood glucose levels from the interstitial fluid using the CGMS. This is a common limitation resulting from the sensor limitation of the CGMS. Although the interstitial glucose level could not completely signify the blood glucose level, it has been shown that the interstitial glucose level with some time lag is highly correlated with the plasma glucose level (1, 17, 28).

In conclusion, we found that the MSE complexity index calculated from the MSE analysis of glucose dynamics was reduced in the diabetic patients compared with that in the control subjects. This suggests that the complexity of glucose dynamics is decreased in diabetes. Such a finding implies the reactivity of glucoregulation is impaired in the diabetic patients. This impairment, which is shown as an increased regularity of glycemic fluctuating pattern, could be detected by MSE analysis.

Perspectives and Significance

This study revealed that diabetes is characterized by an increased regularity of glycemic fluctuating pattern via the MSE analysis of the CGMS data. Future studies could be directed toward elucidating whether the MSE complexity index could be used as a biomarker in the monitoring and the evaluation of the effectiveness with various treatment modalities in diabetes.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

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