Long-range negative correlation of glucose dynamics in humans and its breakdown in diabetes mellitus

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There is growing evidence that physiological signals often display a power-law type negative autocorrelation (2, 6, 19, 20, 30, 37, 38) rather than an exponential one, which would be expected for standard linear negative feedback systems. Although the origins of such long-range negatively correlated dynamics remain largely unknown, it is often associated with a dual antagonistic control mechanism such as the balance of the sympathetic and parasympathetic nervous systems in heart rate control (2, 30, 37, 38) and the antagonistic muscular control of human postural balance (6).

The concentration of glucose in the circulation is more closely controlled than any other fuels (11) and is also regulated based on a balance between the flux (ingestion and/or breakdown) and the reflux (uptake and/or storage), respectively, by hyperglycemic hormones (cortisol, epinephrine, growth hormone, and glucagon) and hypoglycemic insulin (5, 21). Thus, in the present study, we hypothesize that normal glucose dynamics are also characterized by a long-range negative autocorrelation. Specifically, by continuously estimating the blood glucose level from the interstitial fluid in humans and using an extended random walk analysis, namely, detrended fluctuation analysis (DFA) (19), we first demonstrate long-range negative autocorrelation to hold in the “long-range” (>2 h) regime in healthy individuals with normal glucose homeostasis. This indicates that in the long-range regime, the net effects causing temporal changes in glucose concentration are negatively correlated, meaning that the flux is duly compensated for by the reflux, and vice versa.

This glucose homeostasis is known to be impaired in diabetes (15, 34), and an elevated glucose level in the circulation and a subsequent urinary loss—a hallmark of diabetes mellitus—is critical in the development of diabetic complications. In the present study, we further show that patients with diabetes mellitus are associated with positively correlated glucose dynamics in the same regime, indicating that the net effects of the flux and reflux persist for many hours. We suggest that the presence of such an anomalous, long-range positive correlation likely reflects the underlying pathogenic mechanisms of diabetes; that is, the lack of long-term stability of blood glucose and the long-range negatively correlated glucose dynamics are indeed functional in maintaining normal glucose homeostasis.

METHODS

Subjects. Twelve nondiabetic subjects and fifteen diabetes mellitus patients participated in the study. The nondiabetic subjects and diabetes mellitus patients were age-matched with each other; the characteristics of both groups are shown in Table 1. In particular, the body mass index showed no significant difference between the patient and nondiabetic subject groups.

All the nondiabetic subjects were in good health, had no known medical disorders, and took no medication. Except for one, all of the diabetes mellitus patients were being treated with insulin (intensive insulin therapy using mainly ultra-short-acting and ultra-long-acting insulin for nine patients, and conventional insulin therapy using biphasic insulin twice daily for five). Three patients received additional oral hypoglycemic agents (alpha-glucosidase inhibitor for one and biguanide for the other two). The study was approved by the local ethics committee of the Jichi Medical School and the University of Tsukuba, and all of the subjects gave their informed consent to participation.

In this study, we did not distinguish between Type 1 and Type 2 diabetes. The patient group contained more Type 2 diabetes mellitus patients than Type 1 patients.

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Measurements. A continuous glucose monitoring system (CGMS; Medtronic MiniMed, Northridge, CA) was used to monitor subcutaneous cell interstitial fluid glucose levels (13, 24). The battery-operated monitor collects average glucose level measurements every 5 min, providing 288 glucose readings over a 24-h period. In the CGMS, the subjects are required to self-calibrate the interstitial glucose measurements against finger-stick blood glucose measurements (self-monitoring of blood glucose) at least four times a day, avoiding times immediately following meals, insulin delivery, or exercise, when blood glucose is relatively unstable.

The subjects did not participate in rigorous physical activity and did not eat between meals during a one-day measurement period. In addition, they refrained from all forms of caffeine, because caffeine has a nonnegligible effect on glucose levels (10, 22, 26). They were instructed not to have big meals. The subjects followed a consistent daily schedule in their meal times (0800, 1200, and 1800), paying attention to the time they woke up (0600 – 0700), and the time they went to sleep (2100 – 2300) during the measurement period.

DFA. To estimate the correlation property of the glucose fluctuations, we used an extended random walk analysis, namely, DFA (19), defined as follows. First, we integrated the glucose time series, and then we prepared equally sized sliding (one point at a time) windows of length n. For each window, the polynomial trend (linear, quadratic, or higher order; the third order in this study), representing nonstationarity in that window, is fit to the data. The detrended fluctuations F(n) are then calculated as the root-mean-square deviation from the trend in each window, which is summed up for all of the windows covering the entire analyzed time series. The procedure is repeated for different window sizes (i.e., scales) n.

For long-range, power law-correlated signals, the magnitude of the fluctuations F(n) and the window size n have a relationship: F(n) ∼ n^α. The scaling exponent α, quantifying the degree of long-range correlations, can be obtained from the slope of a straight line fit to F(n) ∼ n^α on a log-log plot. Uncorrelated white noise yields α = 0.5 and the Brownian motion—an integrated white noise with uncorrelated increments or changes—yields α = 1.5. Therefore, the long-range negatively correlated fluctuations or changes in glucose level are reflected in α < 1.5 for the absolute glucose measures, while the positively correlated fluctuations are reflected in α > 1.5.

This method yields α estimates (α's) from 288 data points, which are highly correlated with true, predetermined α values—420 samples uniformly distributed within the range of 1.0 ≤ α ≤ 2.0: α's = 1.02α ± 0.02 (correlation coefficient = 0.95, residual standard error = 0.10) for shorter scales n < 22 below the crossover point at n = 22 (Fig. 2), and α's = 1.00α ± 0.03 (correlation coefficient = 0.86, residual standard error = 0.18) for longer scales n ≥ 22.

Mean amplitude of glycemic excursions. Clinically, the tightness of glucose regulation has previously been evaluated based on continuous glucose measurements, by using the mean amplitude of glycemic excursions (MAGE) (28). The MAGE is a measure of within-day glucose instability—that is, the variability of glucose under ambulatory, fed conditions within 24 h. The MAGE parameter gives an indication of “dispersion” of the glycemic patterns of differing configurations. To emphasize the major glucose swings and eliminate minor ones, only glucose excursions that exceed one standard deviation are used for the calculation of MAGE.

We define “absolute” MAGE+/− as an arithmetic mean of either successive increases (MAGE+) or decreases (MAGE−) in glucose levels exceeding one SD of the whole record; the smaller value implies tighter regulation. In this study, all the MAGE values (i.e., MAGE+/−, MAGE+, and MAGE−) were calculated and compared with the scaling exponent-α as defined above.

Statistical analyses. Data were expressed as means ± SD. Differences in the scaling exponents among nondiabetic subjects, diabetes mellitus patients, and the reference α = 1.5, were evaluated by the Student’s t-test. The DFA plots, that is, plots of log10 F(n) vs. log10 n, for the nondiabetic subjects exhibit the so-called “crossover” phenomenon: there exists a difference in the glucose correlation properties between the short- (α1) and the long-range (α2) regimes. These α1,2, as well as the crossover point, were determined for each subject or patient and for each group by the best two-line fit based on the χ2-test and on the Akaike Information Criterion (AIC) (1). The Pearson’s product moment correlation coefficients were calculated for comparisons of the α1,2, the averaged F(n), and the MAGE values.

RESULTS

During a one-day measurement period, the glucose dynamics were measured by the CGMS for each subject. Fig. 1 shows two representative records of glucose dynamics for an age- and gender-matched nondiabetic subject and a type 1 diabetes mellitus patient. The record for the patient shows a day-long excursion in addition to distinct bursts due to meals. In contrast, for the nondiabetic subject the glucose level is generally stable throughout the day, with the exception of small meal-induced bursts. Compared with nondiabetic subjects, the mean glucose level is higher (90.6 ± 7.7 vs. 157.2 ± 49.5 mg/dl, P < 0.01), and the standard deviation is greater (11.6 ± 3.2 vs. 46.5 ± 17.3, P < 0.01) in diabetes mellitus patients.

The DFA plots for all of the nondiabetic subjects (Fig. 2A) and for the group average F(n) (Fig. 2C) exhibit the crossover phenomenon. The individual crossover points fall in a range from 70 to 195 min, while the crossover point for the grouped data occurs at about 2 h. The locations of the crossovers coincide, irrespective of whether they were obtained using the χ2-test or AIC for the crossover criterion. In the short-range
regime (<2 h), the scaling exponent estimated from the group average of slope values is $\alpha_1 = 1.77 \pm 0.32$, meaning that the glucose fluctuations are positively correlated ($P < 0.01$ from $\alpha = 1.5$) for short timescales in healthy subjects. This implies the net effects of glucose flux/reflux persist within these shorter timescales. On the contrary, in the long-range regime (>2 h), the scaling exponent is $\alpha_2 = 1.25 \pm 0.29$, suggesting that the glucose dynamics is negatively correlated ($P < 0.01$ from $\alpha = 1.5$). This means that, in these longer timescales, the glucose level is tightly regulated by a negative feedback mechanism, giving rise to the long-term stability.

The DFA plots for most of the diabetic patients do not show the presence of any crossover phenomenon (Fig. 2B). Although the two-line regression identified a crossover point for the grouped data approximating 3 h, the scaling exponents estimated from the slope values in the short-range regime (<3 h; $\alpha_1 = 1.72 \pm 0.21$) were not statistically ($P > 0.05$) different from those in the long-range regime (>3 h; $\alpha_2 = 1.65 \pm 0.30$). The scale dependency of the group mean $F(n)$ (Fig. 2C) reveals that these exponents are compatible with those of nondiabetic subjects in the short-range regime ($P > 0.05$ for the difference), but significantly ($P < 0.05$) larger in the long-range regime. This suggests that the patients with diabetes mellitus are associated with positively correlated glucose dynamics, even in the long-range regime, indicating that the net effects of the flux and reflux persist for many hours.

The scaling exponent for the patients is significantly ($P < 0.05$) correlated with the MAGE values. However, neither the short- ($\alpha_1$) nor the long-range ($\alpha_2$) exponent for nondiabetic subjects is significantly correlated with the MAGE values (Fig. 3). On the contrary, in nondiabetic subjects, the average log$_{10}$ $F(n)$ for >2 h, that is, the long-term variability in glucose levels, is significantly ($P < 0.05$) correlated with the MAGE values (Fig. 4), while the correlations between the long-term glucose variability and the MAGE values is rather weak in patients with diabetes mellitus. Thus it can be said that the MAGE indices are closely related to a mechanism responsible for the long-range glucose correlation only in diabetes mellitus patients, while they are significantly related to the glucose variability only in nondiabetic individuals.

**DISCUSSION**

The present study investigates fluctuations of glucose using an extended random walk analysis, referred to as DFA (19). The advantage of the DFA method is that it can more accurately quantify the correlation property of original signals, even if masked by nonstationarity (in the form of the quadratic trend in this case—resulting from third-order polynomial detrending applied to integrated time series data) (31), compared with traditional methods such as autocorrelation and/or power spectrum analysis (8). Consequently, it is found that, in nondiabetic subjects, continuous glucose dynamics are positively correlated within timescales shorter than about 2 h, but negatively correlated in longer timescales. On the other hand, patients with diabetes mellitus, although they possess a similar positive correlation to that of nondiabetic subjects in short scales, are associated with a lack of negative correlation at longer scales. This suggests a loss of long-term glucose regulation by a negative feedback mechanism normally resulting from the actions of hyperglycemic and hypoglycemic hormones.

**Long-range correlation.** The scaling exponent $\alpha$ derived by the DFA method reflects the probability of a simultaneous increase or decrease in the variability at two distant points in time in the time series, revealed for all distances up to long-range timescales, hence probing the nature of “switching” patterns between high and low values in a statistical sense. Scaling exponents larger than 1.5 indicate positive temporal autocorrelation or “persistency” in the subsequent increases or decreases, and values lower than 1.5 correspond with negative autocorrelation or “antipersistency”—thus, with a higher likelihood of the switching of direction. In the present study, we find such negatively correlated glucose dynamics only in nondiabetic subjects at a longer timescale than ~2 h.

It is well known that normal glucose homoeostasis is achieved, through a negative feedback regulation, by a tightly
controlled balance between glucose delivery or flux (from the liver in the postabsorptive state and from the gut in the postprandial state) and glucose utilization or reflux (5). The present study further reveals that this tight control is not very effective in the short-range regime but is effective in timescales longer than ~2 h. Indeed, this coincides with the standard recommendation for the evaluation of the blood glucose level 2 h after oral glucose loading (4, 32, 33, 36). After 2 h, compensation for the glucose load takes place in nondiabetic individuals, and the resultant glucose level returns to normal by an effective negative feedback mechanism. For diabetes mellitus patients, however, the glucose level remains high because of an impaired negative feedback regulation reflected in the litus patients, however, the glucose level remains high because of an effective negative feedback mechanism. For diabetes mellitus patients, however, the glucose level remains high because of an impaired negative feedback regulation reflected in the resultant lack of the negative correlation in the longer timescales. Thus we believe that the current results provide deeper insights into the dynamics of long-term glucose homeostasis in health and disease.

It is also of note that the negative correlation observed and characterized by the scaling exponent $\alpha_2$ is of a “power-law” type rather than an exponential one, which would be expected for standard linear negative feedback systems. Thus it can be argued that the normal long-term glucose homeostasis is a nontrivial and far more complex system than that which is explained by the linear feedback regulation. Although diurnal or even circadian variations in the neuroendocrine system, which exert a strong regulatory effect on the carbohydrate metabolism (16), may be related to this phenomenon, an exact mechanism responsible for the power-law antipersistency in healthy glucose dynamics remains unknown. There are further possibilities to explore fundamental aspects of glucose control in terms of models of systems displaying such long-range correlated behavior and in terms of their dynamical properties, as has been done in the case of heart rate variability (2, 19, 20, 30, 37, 38), a thoroughly investigated example of biological complexity showing long-range anticorrelation.

Short-range correlation. Both in nondiabetic subjects and in patients with diabetes mellitus, glucose dynamics in the short-range regime is characterized by the positive correlation or persistency. This persistent pattern implies that the net effects of glucose flux/reflux persist within these shorter scales, presumably as a result of the short-term response to meals or other behavioral effects. In addition, a reported pulsatile pattern of insulin within these scales (9, 21) and the associated persistent glucose excursions might contribute to this phenomenon.

Although the scaling exponents in the short-range regime are not different between patients and controls, the root-mean-square of fluctuation ($F(n)$) of glucose in diabetes mellitus patients is considerably greater than that in nondiabetic subjects (Fig. 2C). Studies revealing disturbed high-frequency pulsatile secretory patterns in first-degree relatives of Type 2 diabetic individuals suggest that an impairment of insulin pulsatility may be an early marker of $\beta$-cell dysfunction (9, 14, 23). In vivo, the $\beta$-cell responds to glucose challenges with characteristic first (within 10 min) and second (>10 min) phase insulin responses (29), and a prominent feature of Type 2 diabetes is a dramatic reduction in the first-phase insulin secretion (7, 35). Thus it is speculated here that the greater magnitude of short-range glucose fluctuations in diabetes mellitus patients might reflect diminished compensatory effects of pulsatile secretory patterns and/or the first-phase insulin secretion on ongoing glucose excursions. This hypothesis should, however, be tested by the direct observation of plasma insulin in further research.

Relationship with MAGE. Various attempts have been made by means of analysis of blood glucose and urinary glucose data to assess the degree of glucose homeostasis and to facilitate monitoring and diagnosis of glucose regulatory system dysfunctions (17, 18, 27, 28). The MAGE is one of the standard clinical indices to measure the tightness of glucose regulation, defined as an arithmetic mean of either successive increases (MAGE+ in our case) or decreases (MAGE=−) in glucose levels exceeding one SD of the whole record. Consistent with a previous report (28), the MAGE of diurnal blood glucose changes in our study is indeed greater in diabetes mellitus patients compared with nondiabetic subjects. Some degree of correlation between the MAGE values and $\alpha_2$ in diabetes mellitus patients should be expected, because a greater level of long-range positive autocorrelation, reflecting the probability of a simultaneous increase or decrease in the variability, should lead to larger glucose excursions, that is, the successive increases or decreases.

However, in nondiabetic subjects, neither the short- ($\alpha_1$) nor the long-range ($\alpha_2$) exponent is significantly correlated with the MAGE values. The likely cause of this lies with the very definition of MAGE: it does not consider excursions below one SD of the record. In other words, in nondiabetic subjects with negatively correlated glucose dynamics in the long-range regime, which counterbalances the excursion gain of the short-range positive correlation, the glucose excursions remain naturally embedded in variability around the mean level. This is why the MAGE indices are in this case more closely related to the magnitude, rather than to the correlation property, of long-term glucose variability. Thus the scaling exponents derived by the DFA method, particularly that for the long-range regime ($\alpha_2$) uniquely identified in nondiabetic subjects, potentially provide deeper insights into the dynamics of glucose.
homeostasis that cannot be captured by a simple threshold-based index like the MAGE.

**Limitations.** There are some limitations to the present study. First, we did not select nondiabetic subjects by using an oral glucose tolerance test to exclude any underlying (slight) abnormality in their glucose control; however, judging from the CGMS records over a period of 1 day, we do not see grounds to diagnose the non diabetic subjects as suffering from impaired glucose tolerance on the basis of fasting glucose levels, postprandial glucose levels, and average glucose levels. Second, in the present study, we opted for diabetes mellitus patients who were severe cases. Thus the estimated difference in glucose correlation properties between the patients and the controls is at its limits. In the future, a comparison will be needed of patients with impaired glucose tolerance and patients with mild diabetes mellitus. Third, we estimated the glucose level from the interstitial fluid. The CGMS is considered capable of accurately tracking acute changes in plasma glucose, but the absolute values for the interstitial glucose concentration are known to be lower than the plasma values (25). The interstitial glucose level with some time lag is highly correlated with the plasma glucose level ($r > 0.9$) (3, 25), which makes alterations in the scaling exponents unlikely. However, the effects of factors, such as glucose diffusion from the capillary, its clearance from the interstitial space, and insulin dependency, should be carefully evaluated in the future.

**Implications.** We have found that the normal long-term glucose homeostasis is maintained by long-range negatively correlated dynamics of the regulatory system. This negatively correlated dynamics is weakened, entirely absent, or even reversed to positive correlation in patients with diabetes mellitus. Owing to recent advances in sensing technologies, continuous and least-invasive data collection for monitoring glucose dynamics, like the CGMS, should be feasible. The present study has emphasized that a state-of-the-art technique of time series analyses such as DFA could be used to monitor and evaluate, in theory in a continuous fashion, the performance of glucose homeostasis in health and disease. It would be intriguing to investigate in a larger study whether the evaluation of the momentary breakdown of long-range negative correlation or the appearance of persistent positive correlation in glucose dynamics could be helpful for better diagnosis and prognosis of patients with diabetes mellitus in a clinical setting.

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