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Research Article

Glucose series complexity in hypertensive patients

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Abstract

Nonlinear methods have been applied to the analysis of biological signals. Complexity analysis of glucose time series may be a useful tool for the study of the initial phases of glucoregulatory dysfunction. This observational, cross-sectional study was performed in patients with essential hypertension. Glucose complexity was measured with detrended fluctuation analysis (DFA), and glucose variability was measured by the mean amplitudes of glycemic excursion (MAGE). We included 91 patients with a mean age of 59 ± 10 years. We found significant correlations for the number of metabolic syndrome (MS)-defining criteria with DFA ($r = 0.233$, $P = .026$) and MAGE ($r = 0.396$, $P < .0001$). DFA differed significantly between patients who complied with MS and those who did not (1.44 vs. 1.39, $P = .018$). The MAGE ($f = 5.3$, $P = .006$), diastolic blood pressures ($f = 4.1$, $P = .018$), and homeostasis model assessment indices ($f = 4.2$, $P = .018$) differed between the DFA tertiles. Multivariate analysis revealed that the only independent determinants of the DFA values were MAGE (β coefficient = 0.002, 95% confidence interval: 0.001–0.004, $P = .001$) and abdominal circumference (β coefficient = 0.002, 95% confidence interval: 0.000015–0.004, $P = .048$). In our population, DFA was associated with MS and a number of MS criteria. Complexity analysis seemed to be capable of detecting differences in variables that are arguably related to the risk of the development of type 2 diabetes. J Am Soc Hypertens 2014;8(9):630–636.

Keywords: Detrended fluctuation analysis; diabetes mellitus; metabolic syndrome; mean amplitude of glycemic excursions.

Introduction

Physiological systems are regulated by complex processes. These systems exhibit nonpredictable, chaotic, nonlinear, and nonstationary behaviors.[1] One of the earliest signs of the dysfunction of a complex system is the simplification of its output. Recently, nonlinear methods, such as entropy estimations and data complexity statistics, have been applied to the analyses of biological signals.[2,3] Such methods have been widely described for the analyses of electroencephalograms,[4] respiratory disorders,[5] cardiac arrhythmias,[6] heart failure,[7] and other types of data.

The level of glucose in the blood is regulated by its flux (ingestion and/or breakdown) and reflux (uptake and/or storage) and is controlled by several hormones and insulin. Most studies of hyperglycemia use the regularity estimator metric known as detrended fluctuation analysis (DFA).[8–11] DFA is a signal regularity measure that estimates the presence of long-range correlations within a time series.

In a previous pilot study, we found that the glucose time series profiles of healthy subjects are more complex (ie, lower DFA) than those of patients with metabolic syndrome (MS) and patients with type 2 diabetes mellitus (DM).[12] A previous study also found that a progressive loss of complexity in the glycemic profile occurs in the short-term range and extends to the long-term range and that

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this loss of complexity is concomitant with the progression from impaired glucose tolerance through mild DM to overt DM.[10] We have also reported that a loss of complexity in the glycemia time series, as evaluated by DFA, is associated with higher mortality in critically ill patients independently of the presence of DM.[13] Thus, we theorized that a loss of complexity in the glycemic profile might be an early and sensitive marker of glucoregulatory dysfunction.

Our aim in the present study was to analyze the relations between glucose complexity and some well-established clinical characteristics that are associated with an increased risk of developing DM in a population with essential hypertension (EH), which is known to be a condition that is associated with an increased risk of diabetes.[14,15]

Methods

Patients

We sought to recruit patients at high risk of developing type 2 DM. Patients were recruited from the General Internal Medicine and Hypertension Outpatient Clinics of the University Hospital of Mostoles, Madrid. The patients who were included in the present study represent the subgroup of patients with EH diagnoses who are part of a larger cohort with an increased risk of developing DM (ie, body mass index (BMI) > 30 or a first-grade relative with type 2 DM and EH). The inclusion criteria for this subgroup were as follows:

1 glycosylated hemoglobin (HbA1c) $< 6.5\%$ and
2 essential hypertension.

The patients were aged between 18 and 85 years. All the patients were evaluated prospectively over a 12-month period. All the patients had a complete medical history and underwent a clinical examination. The blood pressure (BP) of the patients was measured in a seated position after 5 minutes of rest. The BP was measured at least three times by a nurse using an appropriate adult cuff size and an automated reading and recording device (HEM-907; Omron Healthcare Inc., Bannockburn, IL). Patients with persistent systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg, those who were using antihypertensive drugs, and those meeting both of these criteria were considered hypertensive and included in the study. Patients with diagnoses of DM, defined by fasting glucose ≥ 126 mg/dL, patients with glycated hemoglobin $\geq 6.5\%$, and those on antidiabetic drug treatments were excluded.

The patients were classified as having MS based on the Adult Treatment Panel III criteria.[16]

The variability of the glucose time series was measured as the mean amplitudes of glycemic excursion (MAGE), which were calculated with the gluc-complex program (available at http://www.fractal-lab.org/download.html).

This research was approved by the Ethics Committee of the Mostoles University Hospital. Written informed consent was obtained from each patient.

The present article reports the basal characteristics of the hypertensive patients included during the first year.

Glucose Time Series

We sought to record 48–72 hours of unrestricted, normal life from each patient. An iPro was inserted into each patient at 8:00 AM. Two hundred eighty-eight consecutive readings (24 hours) were selected for analysis. When possible, the time series began at 8:00 AM on the second day of recording. However, when default readings were found in this time series, the times series was shifted to avoid missing values. One or two consecutive missing values were corrected by interpolation. When more than two consecutive values were missing, the time series was deemed unsuitable.

Detrended Fluctuation Analysis

Complexity was assessed with DFA. An in-depth discussion on DFA is beyond the scope of this article, and such discussions can be found elsewhere.[13,17]

DFA is a unitless metric that estimates the degree of long-range correlations within a signal by analyzing how the time series and its linear regression diverge as the considered ''time window'' increases. Intuitively, DFA can be conceived a representation of the span of the influences of different points in a time series. In a highly complex series, the influence of each point rapidly fades away, whereas in a ''smoother'' series, the influence of each point lasts longer. As a general rule, higher complexities are represented by lower DFA (until the minimum value of 0.5). DFA values <0.5 indicate anticorrelations, which also imply some degree of predictability and thus a lower level of complexity.

Statistical Analyses

The differences between groups were evaluated with *t* tests analyses of variance, and post hoc analyses (Tukey tests) were used when necessary. When the data were not normally distributed, as determined by the Kolmogorov–Smirnov test, the Kruskal–Wallis test was employed. Correlations between continuous variables were analyzed with Pearson correlations when the variables were normally distributed and with Spearman correlations when the distributions were not normal or the data were discrete (ie, the number of fulfilled adult treatment panel III metabolic syndrome criteria). Linear regressions were used to correlate DFA with the other variables with known influences on glucose metabolism.

The complexities of the glycemic profiles, measured as the DFA, followed a normal distribution as confirmed by