Cyclical Variation in HbA1c Values During the Year: Clinical and Research Implications

The association between glycated hemoglobin (HbA1c) and long-term diabetes complications is well established (1). Although HbA1c is a key process and outcome measure in clinical and research settings, reporting varies from single annual measurements to an average of interval settings, reporting varies from single annual outcome measure in clinical and research trials (2). Previous seasonal variability studies have used small datasets and short time intervals. Six equidistant samples are required to describe a cycle of seasonal variation, which means that a minimum dataset of 3 years is required.

We examined seasonal variation using HbA1c measurements collected quarterly from children aged 2-21 years (mean 12.9 years) attending a single clinic between 1999 and 2012. HbA1c was measured using the Diabetes Control and Complications Trial-aligned DCA1000 (Siemens Healthcare Diagnostics Inc., Deerfield, IL). Bias was determined over the HbA1c range 5.0-10.9% (31-96 mmol/mol) using the U.K. External Quality Assessment. The scheme over the time period was −0.08%.

A total of 5,140 measurements (average 3.6 measurements/patient/year) were collected and coded for the months January-March, April-June, July-September, and October-December. The data were then subjected to time series analysis. The clinic size increased from 22 to 356 between 1999 and 2012, with a decline in the median HbA1c from 10.2 to 7.7% (88-61 mmol/mol). The percentage of the clinic with HbA1c < 7.5% (58 mmol/mol) increased from 9.7 to 40.8%. Insulin pump therapy increased from 0 to 77% of the clinic and was associated with a lower median HbA1c level (7.5%; 58 mmol/mol) than with the multiple daily injection regimen (8.8%; 73 mmol/mol; P < 0.001), and a lower SD (1.2%; 13.1 mmol/mol) than the multiple daily injection regimen (2.0%; 21.9 mmol/mol).

The data were stationarized (i.e., the difference plus the mean) prior to analysis to remove the trend of continuous decline in HbA1c, which interferes with the precise identification of oscillations. Fourier transformation was then used to determine oscillations within the time series (Fig. 1) (3). The decimal precision of oscillations is robust and provides the best evidence to date of this phenomenon. The use of stationarization to eliminate trends in the data adds to the strength of this study. The submission of data to quality-improvement schemes should be based on the average for the individual over the whole year. The clinical trial design should include estimates of HbA1c seasonal variation to avoid types I and II statistical errors.

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Online Letters

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