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SYMPOSIUM

Increases in Whole Blood Glucose Measurements Using Optically Based Self-Monitoring of Blood Glucose Analyzers Due to Extreme Canadian Winters

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Abstract

Background:

Temperature and humidity have been reported to influence the results of whole blood glucose (WBG) measurements.

Methods:

To determine whether patient WBG values were affected by seasonal variation, we conducted a retrospective analysis of 3 years' worth of weekly averages of patient WBG in five Edmonton hospitals.

Results:

In all five hospitals, the winter WBG averages were consistently higher than the summer WBG averages, with the differences varying between 5% and 9%. Whole blood glucose averages were negatively correlated with the outside temperature. This seasonal variation was not observed in weekly patient averages of specimens run in a central hospital laboratory.

Interpretation:

It is probable that the seasonal variation of WBG arises from the very low indoor humidities that are associated with external subzero temperatures. These increases in WBG in cold weather may be due to limitations in the WBG measuring systems when operated in decreased humidities and/or increased evaporation of the blood sample during the blood glucose measurement process. The implications of this seasonal variation are significant in that it (1) introduces increased variability in patient WBG, (2) may result in increased glucose-lowering therapy during periods of external cold and low indoor humidity, and (3) confounds evaluations of WBG meter technology in geographic regions of subzero temperature and low indoor humidity. To mitigate the risk of diagnosing and treating factitious hyperglycemia, the humidity of patient care areas must be strictly controlled.

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Abbreviations: (ADA) American Diabetes Association, (EGH) Edmonton General Hospital, (GNH) Grey Nuns Hospital, (HbA1c) glycohemoglobin A1c, (MGH) Misericordia General Hospital, (RAH) Royal Alexandra Hospital, (SD) standard deviation, (SMBG) self-monitoring of blood glucose, (UAH) University of Alberta Hospital, (WBG) whole blood glucose

Keywords: diabetes, environmental effects, humidity, whole blood glucose monitoring

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Introduction

Self-monitoring of blood glucose (SMBG) forms the basis of tight glucose control in patients with type 1 diabetes, gestational diabetes, and insulin-requiring type 2 diabetes.[1,2] The role of SMBG is more controversial in patients with type 2 diabetes who require only oral hypoglycemic or nutritional therapy. The growth of glucose testing is extraordinary; for example, in Saskatchewan, the number of test strips purchased by provincial government tripled between 1996 and 2005.[3] In fact, the province of Saskatchewan's expenditures for reagent strips is second only to that for Lipitor.[3] Much of the growth in glucose testing can be attributed to the rapidly growing population of patients with type 2 diabetes.[3]

Because important decisions such as insulin dosing are linked to glucose measurements, it is important that the accuracy of SMBG devices be optimal. Several professional organizations have attempted to define usable maximum limits for SMBG measurement error. In 1987, the American Diabetes Association (ADA) recommended that SMBG systems achieve a total error (analytical plus user) of <10% at glucose levels between 30 and 400 mg/dl (1.7 and 22.2 mmol/liter).[4] In 1996, the ADA revised the performance goal to a more stringent analytical error of <5%.[5] Unfortunately, the ADA did not completely specify the experiments to measure SMBG performance; as such, the performance goals could not be applied easily. Although accuracy is desirable at any glucose level, it is our opinion that this accuracy is most crucial for blood glucose concentrations that are close to or within the hypoglycemic range.[6]

In 2001, the International Organization for Standardization proposed criteria for glucose meter accuracy that accounts for the importance of reliable glucose results in the hypoglycemic range. They proposed that, for a reference glucose value of ≤75 mg/dl (4.2 mmol/liter), the meter reading should be within 15 mg/dl (0.8 mmol/liter), and for a reference glucose value of >75 mg/dl (4.2 mmol/liter), the meter reading should be within 20%.[7]

In Edmonton hospitals, the vast majority of whole blood glucose (WBG) measurements were performed with the SureStep®Flexx. (LifeScan, Milpitas, CA). The manufacturer's suggested environmental operating limits are temperature ranges of 18 to 30 °C and relative humidity ranges of 30% to 70% (noncondensing).[8] The manufacturer states that testing outside these ranges may cause inaccurate results. Nurses operate this instrument according to standard operating procedures and measure two levels of quality control product each day of use. The nurse operation of the SureStepFlexx is supervised by the Point of Care division of the Department of Laboratory Medicine and Pathology, University of Alberta Hospital (UAH).

It is standard practice in North American clinical laboratories to verify the performance of new lots of analytical reagents before they are routinely used. In Edmonton, new lots of SureStepPro WBG reagent strips are validated using eight different samples of fresh whole blood. Immediately following WBG testing, the whole blood is centrifuged and the resultant plasma glucose is analyzed with the laboratory chemistry analyzer. A SureStepPro reagent lot is rejected if the average difference between the SureStepFlexx WBG monitor readings and the chemistry analyzer values exceeds 10% (no hematocrit corrections are attempted). Over the past 5 years, SureStepPro reagent strip lots seemed to exhibit borderline (but acceptable) performance during winter evaluations compared to summer evaluations of new reagent lots. Furthermore, the glucose concentrations for the quality control solutions were consistently higher in the winter months. Based on these observations, we conducted a retrospective study of patient WBG values at five hospitals in Edmonton, Canada.

Materials and Methods

During the 3-year study period from November 1, 2002, to October 31, 2005 (156 weeks), 19 different lots of SureStepPro reagent strips were used. No single lot accounted for more than 14% of the WBG results.

Patient WBG results were collected from five geographically separate hospitals in the Edmonton area: a major academic hospital, UAH; a tertiary care hospital, Royal Alexandra Hospital (RAH); and three general hospitals, Edmonton General Hospital (EGH), Grey Nuns Hospital (GNH), and Misericordia Hospital (MGH). Crystal Reports XI (Business Objects, San Jose, CA) was used to identify patient WBG results from the five hospitals for the study period. Whole blood glucose results were excluded from averaging (truncated) if they

exceeded 12.5 mmol/liter or were less than 2.5 mmol/liter (previous work by the author [Cembrowski] describes the use of averages of patient data to detect significant trends, and averaging truncated data permits easier trend detection[9]). Truncated WBG data for each week were averaged for each hospital to determine weekly averages. Weekly averages were also calculated from patient plasma and serum glucose that were analyzed at the UAH core laboratory with two LX-20 chemistry analyzers (Beckman Coulter, Fullerton, CA). Hourly temperatures at the Edmonton International Airport were obtained from the Environment Canada weather archive Website (*http://climate.weatheroffice.ec.gc.ca/climateData/canada_e.html*). These measurements were used to determine weekly averages of external temperature.

From January 11 to 31, 2008, during subzero weather, a humidity-logging device was used to monitor the average weekly humidity sequentially in patient care units at UAH (first and third week) and RAH (second week). The calibration of this device was checked with the Vaisala HM141 humidity and temperature indicator (Vaisala Oyj, Helsinki, Finland).

Data were analyzed using StatGraphics Plus, version 2 (StatPoint, Inc., Herndon, VA). Simple linear regression analysis was performed for WBG measurements at each hospital and the core laboratory against the weekly average external temperature. Linear regression graphs were created using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, CA, *www.graphpad.com*).

Results

Of the roughly 2.75 million WBG tests, WBG results less than 2.5 mmol/liter (n = 23,875) and greater than 12.5 mmol/liter (n = 414,830) were excluded from the analysis,[9] resulting in approximately 2.32 million WBG results. **Figure 1** shows the relationship between the weekly external temperature and WBG testing at each of the participating Edmonton hospitals and the UAH core laboratory. **Table 1** lists the average and maximal WBG changes at each hospital and the plasma glucose readings at the UAH core laboratory. In all five hospitals, the winter WBG averages are consistently higher than the summer WBG averages, with the differences varying between 2% and 5% (calculated by regression equation) and the maximum differences varying between 5% and 9% (obtained by visual estimation). The lack of a correlation (r^2 = 0.000) between the external temperature and the core laboratory values suggests that the effect is limited to the WBG testing and is not due to physiological seasonal variations affecting patient glucose. **Table 2** lists the linear regression data for each individual hospital and the UAH core laboratory.

Between January 11 and 31, 2008, the data-logging device indicated average (standard deviation [SD]) weekly relative humidities of 23.3% (1.45), 10.8% (2.05), and 25.6% (2.61) in the patient care areas. During this time, the external temperatures varied between -44 and 0 °C and weekly averages (SD) were -9 °C (4.12), -13 °C (2.23), and -21 °C (11.21).

Table 1.
Changes in Whole Blood Glucose Averages at Five Edmonton Hospitals

Hospital	Year of hospital construction	Glucoses averaged weekly (n)	Glucose average (mmol/liter)	Regression Analysis		Visual Analysis	
				Average glucose change (mmol/liter)	Average glucose change (%)	Maximum glucose excursion (mmol/liter)	Maximum glucose excursion (%)
UAH	1981–1986	4900	7.82	+0.20	+2.5	+0.4	+5.1
RAH	1958–1994	4474	7.55	+0.22	+3.0	+0.4	+5.3
EGH	Pre-1960	624	7.83	+0.17	+2.2	+0.7	+8.9
GNH	1988	1281	7.37	+0.18	+2.4	+0.5	+6.8
MGH	1969–1991	1288	7.66	+0.37	+4.8	+0.5	+6.5
UAH core lab	1982	893	7.00	-0.01	-0.1	—	—

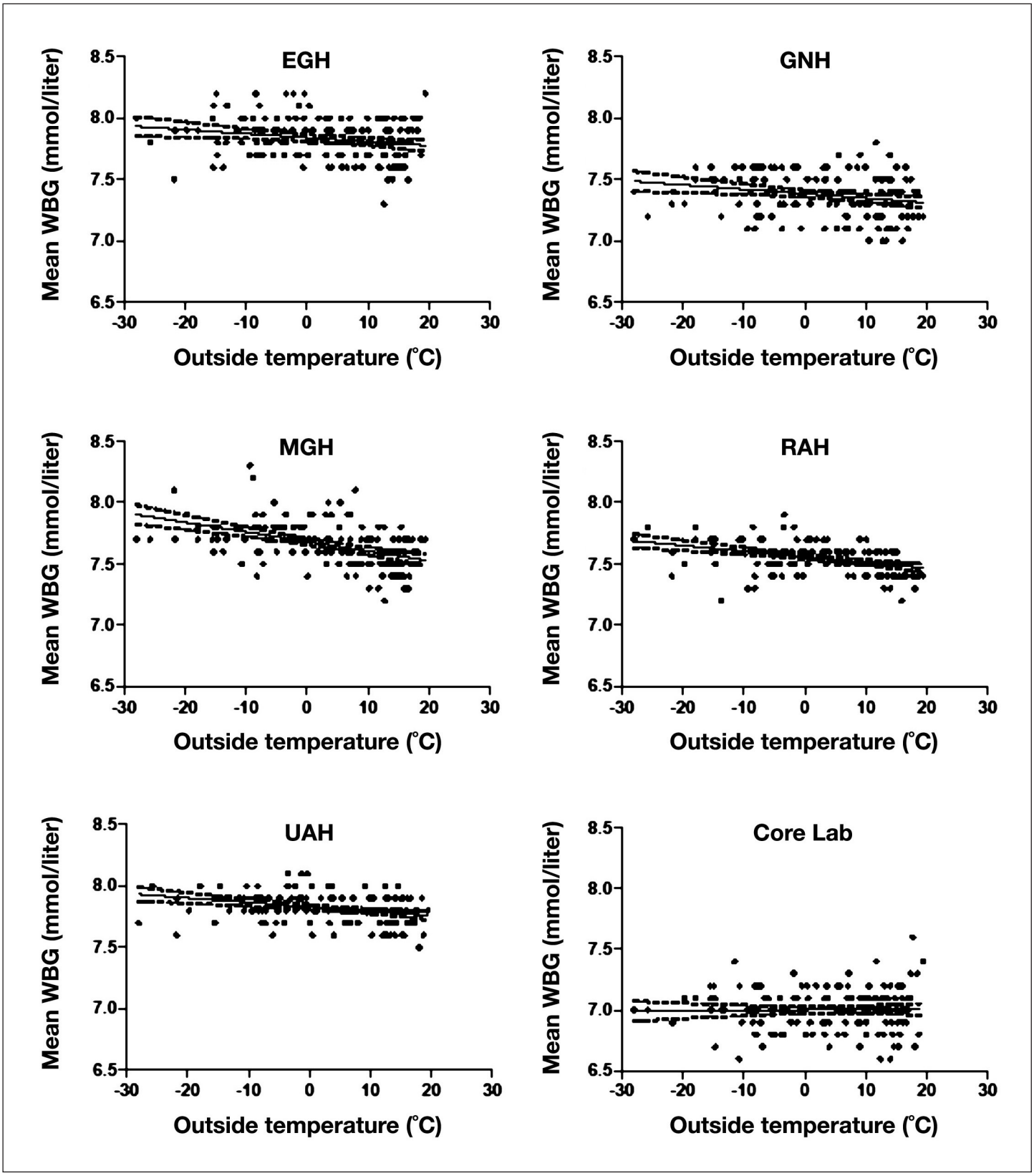

Figure 1. Linear regression analyses of average weekly external temperatures and average weekly patient glucose at five Edmonton hospitals and the core laboratory (156 weeks).

Table 2.
Linear Regression Models for the Effect of Temperature on Weekly Whole Blood Glucose Averages at Five Edmonton Hospitals and the Core Laboratory

Hospital	*n*	Slope	y intercept	Correlation coefficient (*r*)	Coefficient of determination (r^2)
UAH	727,292	-0.003980	7.835	-0.359	0.129
RAH	662,241	-0.004499	7.560	-0.405	0.164
EGH	92,798	-0.003403	7.841	-0.230	0.053
GNH	189,549	-0.003533	7.386	-0.235	0.055
MGH	190,607	-0.007304	7.682	-0.451	0.203
UAH core lab	132,664	0.000219	7.001	0.015	0.000

Interpretation

Edmonton is a landlocked northern Canadian city located at the 53rd parallel with an altitude of 668 m. Outside average weekly temperatures can vary from -25 °C in the winter to +20 °C in the summer. Edmonton winters are extreme, as evidenced by the external temperature graphs in **Figure 2**. In harsh winter climates, achieving optimal indoor humidity (at least 30% for operating rooms[10] and around 40% for sickrooms[11]) is difficult, as heating to the lower range of human comfort (18 °C) reduces ambient indoor humidity to below 20% for part of the winter.[12] Adding moisture to this air causes condensation on the walls, roofs, and windows and results in mold growth and structural damage, including metallic corrosion and wood rot. For this reason, relative humidity levels of 20% during the winter season are common in northern hemisphere hospitals, including those in Sweden,[13] Norway,[14] Turkey,[10] and Japan.[11] The low relative humidities documented in the UAH and RAH patient care areas in January 2008 are consistent with these northern hemispheric findings.

Our finding of increased WBG values in the winter months is probably due to at least two different factors. First, in a low-humidity environment, any delay in testing will be accompanied by rapid evaporation of the blood, with resultant concentration of glucose in the sample. In an attempt to replicate this phenomenon, in January 2008 (relative humidity was 21.5% and room temperature was 20.7 °C), five samples of whole blood (20 µl) were applied to fingertips of a volunteer from which glucose concentrations were serially measured. The average glucose increased by approximately 6% when measurement was delayed 1 min.

Second, instrument-associated factors may also cause the increased blood glucose. As the blood drop is applied to the porous material on the blood measuring strip, evaporation probably occurs on this material, which again results in concentration of the sample.

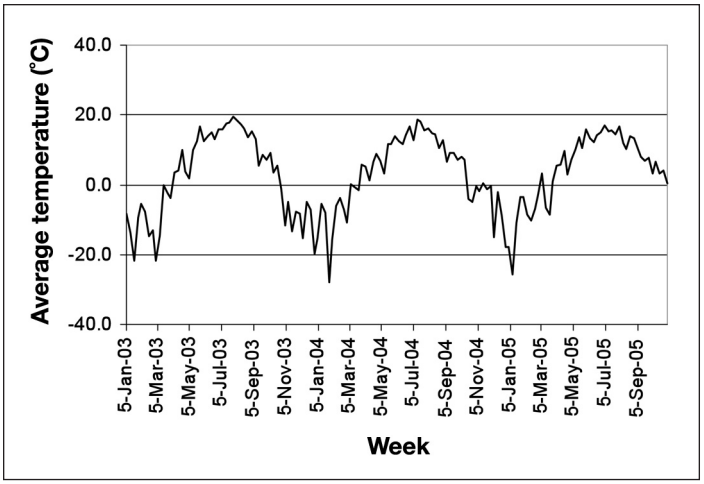

Figure 2. Weekly average external temperatures in Edmonton, Alberta, Canada.

This 3-year retrospective study documents seasonal increases in average WBG between 2% and 5% (determined from the regression equation) and maximum average differences varying between 5% and 9% (determined visually). Because these are average differences, some individual patient differences were probably much higher than 9% and would be due to a combination of the humidity-dependent bias and other sources of error, both random and systematic.[15]

These environment-related WBG errors may not be significant in ambulatory patients who are well controlled and do not modify their insulin therapy excessively. On the other hand, newly diagnosed patients or patients who regularly modify their insulin dose based on WBG values could be puzzled by sporadic or unexpected increases WBG during the winter. Hopefully, unexpected WBG increases will prompt resampling and remeasurement rather than modifications in insulin doses.

Environment-related WBG errors may be more important for critically ill patients and will depend on the institutional definition of hyperglycemia in these patients. Until the publication of the NICE-SUGAR investigation,[16] prior studies had suggested that maintenance of glucose within the "tight" range of 4.4 to 6.1 mmol/liter[17,18,19] could prevent both short- and long-term adverse effects of elevated glucose in the critically ill. The adoption of intensive insulin therapy to maintain glucose levels within this "tight" range was becoming widespread for critically ill patients.[20,21] It is therefore possible that some critically ill patients would be inadvertently overtreated for artificially increased glucose during periods of subzero weather (and low humidity). It is essential that nursing staff performing WBG tests on critically ill patients be aware of this potentially confounding effect. Patient care areas with good humidity control should not demonstrate these environmental-related glucose increases. During subzero weather, patient care areas with inadequate humidity control should confirm unexpected elevations in WBG values with other methods, such as point-of-care blood gas instruments that are equipped with glucose-measuring electrodes.

These seasonal variations in blood glucose have other implications. As manufacturers usually optimize their meter performance for humidities between 30% and 60% prior to acceptance into clinical operation, meters should be tested for performance during seasonal extremes in areas that experience conditions outside the manufacturers specifications.

Seasonal variation has been reported in glycohemoglobin A1c (HbA1c) of Japanese patients with type 2 diabetes, with HbA1c values being highest in winter months and lowest in summer through fall.[22] Even healthy subjects may exhibit seasonal variation in HbA1c values.[23] We did not observe this variation in our hospitalized patients who had their glucose measured by the core laboratory (r^2 = 0.000). It is possible that this normal seasonal intraindividual variation is obscured by the stress hyperglycemia in the ill patient.

Other authors have investigated the effect of temperature and humidity on the performance of multiple WBG systems. Most of these studies have examined the effects high altitude alone,[24] a combination of low humidity and high altitude,[25] temperature and high humidity,[26] or temperature and high altitude[27] on WBG system performance. To our knowledge, this is the first report to compare actual seasonal temperature fluctuations with WBG values of unmodified patient samples.

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