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SYMPOSIUM

Variation in the Frequency of Hemoglobin A1c (HbA1c) Testing: Population Studies Used to Assess Compliance with Clinical Practice Guidelines and Use of HbA1c to Screen for Diabetes

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Abstract

Background:
The volume of hemoglobin A1c (HbA1c) testing has increased dramatically over the past decade and few studies have attempted to determine how the test is used. The goals of this study were to evaluate the frequency of HbA1c testing in regional populations to assess the extent of screening for diabetes and to determine if the HbA1c testing intervals of known diabetic patients were consistent with clinical practice guidelines.

Methods:
Two years of HbA1c results were extracted from laboratory information systems in four regions of the province of Alberta that represent urban, mixed urban–rural, and rural populations. HbA1c testing frequencies and the proportions of nondiabetic patients undergoing HbA1c tests were derived.

Results:
Approximately 60% of HbA1c tests in each region were done on patients who had only a single test during the 2-year interval. Testing of nondiabetic patients accounted for 24% of HbA1c tests and varied by region. While the cumulative frequency distributions of HbA1c test intervals resembled each other, detailed analyses of the frequency distributions depicted broad multimodal peaks and regional variations that suggest a great deal of heterogeneity among practices. The most common HbA1c testing interval was 3 months ± 3 weeks in each region and is consistent with the 3-month test interval target in a clinical practice guideline.

Conclusions:
HbA1c testing is being performed on a substantial proportion of nondiabetic patients. On average, patients with diabetes in Alberta receive 1.5 HbA1c tests per year. However, we observed regional differences in the frequency of testing and variation in compliance with clinical practice guidelines.

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Abbreviations: (ADA) American Diabetes Association, (CDA) Canadian Diabetes Association, (HbA1c) hemoglobin A1c

Keywords: diabetes mellitus–blood, diabetes mellitus–diagnosis, glycated hemoglobins, screening, utilization

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Introduction

Since the publication of results of the Diabetes Control and Complications Trial in 1992,[1] the use of hemoglobin A1c (HbA1c) measurements to assess glycemic control in patients with diabetes has become a focal point of clinical practice guidelines for diabetes and well integrated into medical practice. The volume of HbA1c testing conducted by clinical laboratories has increased dramatically over the past decade and few studies have attempted to determine how the test is being used. Both the American Diabetes Association (ADA) and the Canadian Diabetes Association (CDA) guidelines have set treatment goals based on HbA1c quantification; however, there is no consensus on the optimal frequency of HbA1c measurement.[2,3] The ADA recommends measurement of HbA1c at least twice yearly in stable patients and more frequently in unstable patients or those undergoing changes in therapy. The CDA recommends that HbA1c be measured every 3 months. Neither the ADA nor the CDA guidelines recommend HbA1c as a screen for diabetes or as a basis for the diagnosis of diabetes. It is possible to detect diabetes with the HbA1c test,[4] and the high volumes of HbA1c tests performed by clinical laboratories across North America suggest that nondiabetic patients are often tested.

Previous studies conducted by Otto and colleagues[5] showed overutilization of HbA1c, with some patients tested up to 28 times in a 1-year period. Because some patients with diabetes were tested only once in a 2-year period, there was also evidence of underutilization of the test. Overall the cumulative frequency of HbA1c testing observed in Alberta by Tran and associates[6] and in Ontario by van Walraven and Raymond[7] and Woodward and colleagues[8] was very similar, which suggests that the utility of HbA1c testing may be similar in different provinces of Canada.

The goals of this study were to evaluate the frequency of HbA1c testing in regional populations to assess the extent of screening for diabetes and to determine if the HbA1c testing intervals of known diabetic patients were consistent with clinical practice guidelines. To assess HbA1c utilization, we examined utilization in the urban populations of Edmonton and Calgary, in the mix of rural and urban dwellers in Red Deer, and in the largely rural population of Wetaskiwin.

Methods

Study Areas

Alberta is a western Canadian province with a population of 3.2 million. During the study period, health services were administered through nine health regions. This study included three health regions that represented 70% of the provincial population (Edmonton: Capital health region, Calgary: Calgary health region, Wetaskiwin and Red Deer: David Thompson health region).

Hemoglobin A1c Methods

Hemoglobin A1c testing in the Capital health region was performed by Bio-Rad Variant II (Hercules, CA) by two clinical laboratories: University of Alberta Hospital (a quaternary care hospital with a large endocrine service) and DynaLIFEDx (an outpatient laboratory serving a large proportion of family physicians). HbA1c testing in the Calgary health region was performed by Integra 700 (Roche Diagnostics, Laval, QC, Canada) by Calgary Laboratory Services. HbA1c testing in the David Thompson health region was performed by Integra 400 (Roche Diagnostics, Laval, QC, Canada) in Wetaskiwin and by Dimension RxL (Siemens Healthcare Diagnostics Inc., Toronto, ON, Canada) in Red Deer.

In these regions, clinical laboratory services (e.g., HbA1c testing) were only provided by the laboratories that participated in the study and no alternate or competing laboratories provided HbA1c analysis to the regional populations.

Data Extraction

Two years of HbA1c data were abstracted from the data repositories of Calgary (3/1/2005 to 3/31/2007 study dates; population of ~1.1 million), Edmonton (2/3/2002 to 10/27/2004; ~1.0 million), Red Deer (1/1/2006 to 12/31/2007; ~91,000), and Wetaskiwin (1/2/2006 to 12/31/2007; ~11,700), Alberta, Canada.

Estimation of the Proportion of HbA1c Testing for Nondiabetic Patients

The proportion of nondiabetic patients that had one HbA1c test per year was derived from data shown in **Figure 2**. The average level of HbA1c in patients that had

more than three HbA1c tests per year (all locations) was 7.33%. It was assumed that the population of diabetic patients in all regions had a mean HbA1c of 7.33%. The mean level of HbA1c in nondiabetic patients was assumed to be 5.2% (midpoint of the HbA1c reference interval of 4.3–6.1%). The number of nondiabetic and diabetic patients was solved algebraically using systems of equations (see later). The number of diabetic and nondiabetic patients with one, two, or three HbA1c tests/2 years was determined for each region, and patients with more than three HbA1c tests/2 years were assumed to be diabetic. A calculation worksheet is available from the authors on request. For example (n_D, diabetic patients; n_{ND}, nondiabetic patients):

$$n_D + n_{ND} = \text{total number of patients with 1 HbA1c test/2 years} \quad (1)$$

$$\frac{n_D \times (7.33\%\ \text{HbA1c})}{n_D + n_{ND}} + \frac{n_{ND} \times (5.2\%\ \text{HbA1c})}{n_D + n_{ND}} = \frac{\text{Observed \% HbA1c in patients with 1 HbA1c test / 2 years}}{} \quad (2)$$

Hemoglobin A1c Testing Intervals

For each patient, the individual time interval between sequential HbA1c tests (separation interval) was determined and collected.[6] The frequency of each separation interval (ranging from 0 to 400 days) was then determined. By dividing the frequency of each separation interval by the total number of repeated test intervals, we derived the relative frequency.

Results and Discussion

A total of 542,504 HbA1c tests were extracted from laboratory information systems in the three study regions over a 2-year interval. The prevalence of diabetes in the province of Alberta was determined to be 3.4%.[9] These extracted data consisted of 1.0 HbA1c tests per different patient per year. If all the HbA1c tests were performed on known diabetic patients, the test frequency would be well below both the ADA guideline of testing at least twice per year and the CDA guideline of four tests per year. It is unlikely that the HbA1c tests were conducted exclusively on patients with diabetes; consequently, a more detailed analysis was performed.

Figure 1 depicts that 54–62% of the total HbA1c test volume in each region was performed on patients that had only one test in the 2-year interval. This high proportion was quite consistent among the four regions and could be attributed to either very poor compliance with the diabetes practice guidelines or common use of the test on nondiabetic patients, possibly to screen for diabetes. The fact that Edmonton had the lowest number of single tests might be associated with the interpretive report printed with any normal HbA1c in Edmonton maintaining that the test should not be used to screen for diabetes.

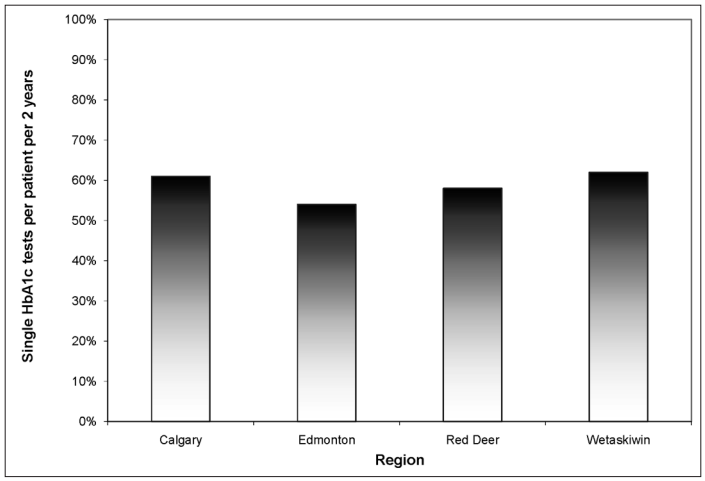

Figure 1. Proportion of HbA1c tests performed once per patient in the 2-year study interval in each region.

The frequency distribution of HbA1c tests per patient in the 2-year study period is depicted in **Figure 2** and is plotted with the mean HbA1c value observed in each frequency group. The distributions and changes in HbA1c are remarkably similar across the regions. As the number of HbA1c tests per patient increases above three, the mean level of HbA1c reaches a plateau. This plateau represents the mean level of HbA1c in patients with diabetes (approximately 7.3% HbA1c), who receive the highest frequency of tests per patient. It is also clear that patients who have only one HbA1c test in the 2-year interval have a lower mean HbA1c level in each region. This downward shift in the mean HbA1c level indicates that this group of patients likely consists of both diabetic and nondiabetic patients. The number of nondiabetic patient tests required to depress the mean HbA1c level to the observed values is calculated algebraically and is shown in **Table 1**.

Table 1 lists the volume of HbA1c tests performed in each region and estimates of the extent of testing in nondiabetic patients. The most striking observation is that use of the HbA1c test in nondiabetic patients consumes a large percentage of the total test volume (18 to 34%). The point estimates of the percentage of HbA1c tests performed on nondiabetic patients are based on a series of assumptions: that the populations of nondiabetic patients have a distribution of HbA1c values represented by the HbA1c reference interval with a midpoint of 5.2% HbA1c and that the distribution of

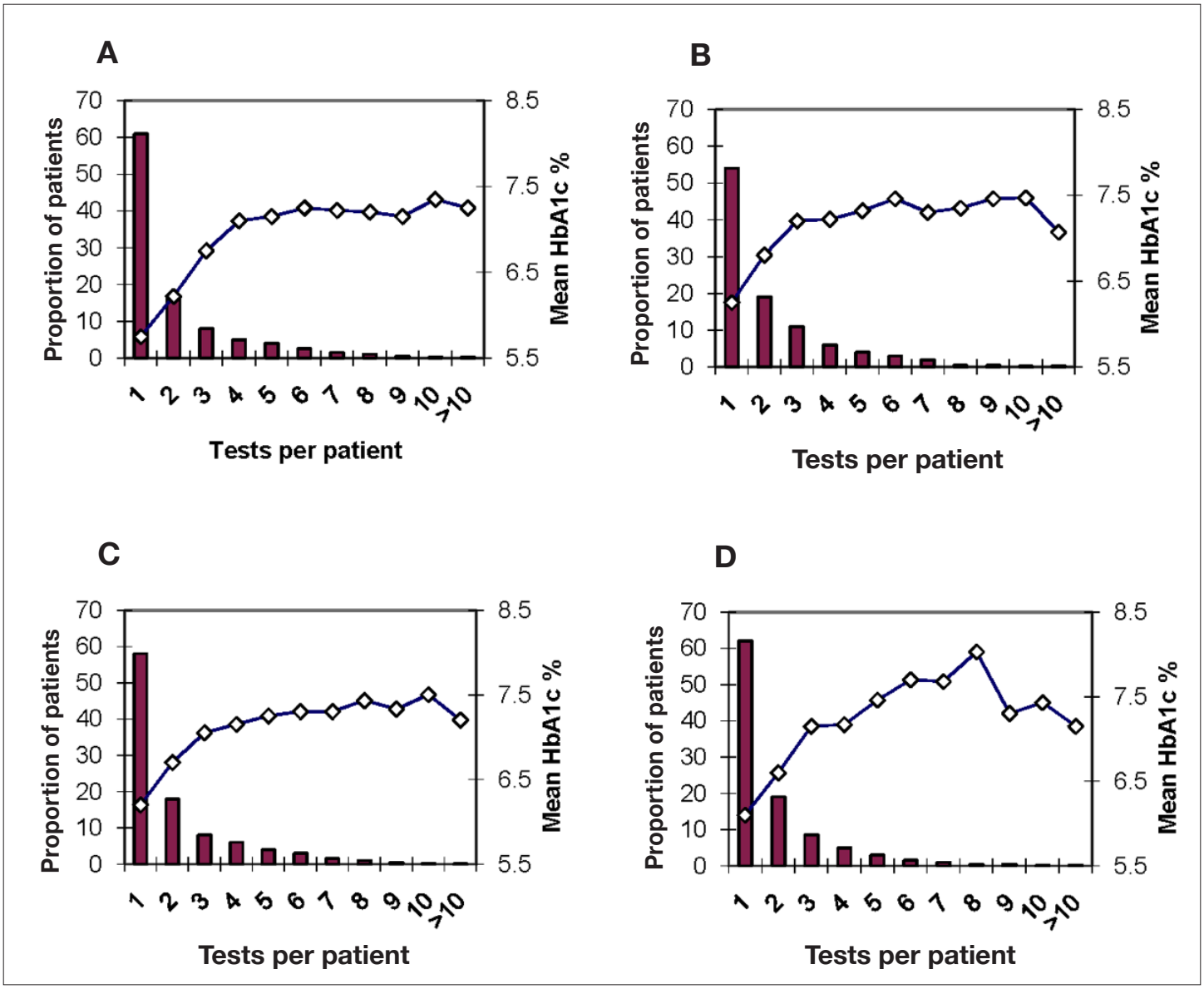

Figure 2. Distribution of tests per patient in the 2-year study interval by region. The mean HbA1c for each group is overlaid. (**A**) Calgary, (**B**) Edmonton, (**C**) Red Deer, and (**D**) Wetaskiwin.

Table 1.
Estimation of Biennial Volume of Nondiabetic Patient HbA1c Testing by Region

	Calgary	Edmonton	Red Deer	Wetaskiwin
Biennial volume of HbA1c tests	317,115	186,077	36,397	12,915
Volume of different patients tested	152,608	90,720	17,540	7,049
Volume of patients with one HbA1c test/ patient/2 years	90,459	48,283	10,149	4,314
Estimated volume of nondiabetic patients tested in 2 years	85,897	29,507	6,208	2,980
Estimated proportion of all HbA1c tests performed on nondiabetic patients	34%	18%	19%	27%

diabetic HbA1c values did not vary with frequency of testing. In our opinion, these point estimates are crude and conservative indicators of differences in practice occurring in each region. In clinical practice, nondiabetic patients tested would be suspected of having a disorder of carbohydrate metabolism and their mean HbA1c level would be higher than the midpoint of the reference interval. By using the midpoint of the reference interval in the calculations, data in **Table 1** underestimate the extent of testing nondiabetic patients tested. For example, increasing the mean HbA1c level among nondiabetic patients from 5.2 to 5.5 or 6.0% for Calgary data alters the estimated proportion of tests used for nondiabetic patients from 34 to 39 and 44%, respectively. Although these are conservative estimates, it was clear that HbA1c testing on nondiabetic patients is a common practice throughout the province, with noticeable regional variation. The Edmonton laboratories had added the following interpretive comment: "*HbA1c should be used to monitor glycemic control only in patients known to have diabetes. It is inappropriate to use HbA1c to screen for diabetes in asymptomatic patients*" when the HbA1c was below the midpoint of the reference interval. The intent of the comment was to dissuade ordering clinicians from using HbA1c to screen for diabetes. Although the estimates of nondiabetic testing in this analysis are crude, it is possible that this interpretative comment was effective at dissuading screening because a lower proportion of nondiabetic patients was tested in the Edmonton region than in the other large urban region, Calgary.

The observations in **Table 1** suggest that HbA1c is widely used in nondiabetic patients, possibly as an aide to screen or diagnose diabetes, and these practices are not advocated in the current ADA or CDA guidelines. This analysis allowed removal of nondiabetic patient data, and subsequent reestimation of the frequency of HbA1c testing was an average of 1.5 HbA1c tests per year per diabetic patient.

To analyze the intervals between HbA1c tests, patients with only one HbA1c test during the study period were removed from the data set and the frequency distribution of HbA1c testing intervals in days was plotted as a histogram in **Figure 3**. This complex distribution for a single region shows a spike-like surge at 7-day intervals superimposed on multiple modes at day 31, 91, and 183. The spike-like surge is attributed to the tendency of patients to habitually have phlebotomy on the same days of the week (Monday–Monday, Saturday–Saturday). To reduce the complexity of data, the relative frequency of HbA1c testing at weekly intervals was determined and then plotted in **Figure 4**. This analysis shows several qualitative differences in diabetic patient management among the four regions. If the CDA guidelines were strictly followed and HbA1c testing occurred four times each year, a single mode at 3 months (16 weeks) would be prominent. It is clear that patients were tested at 1-, 3-, and 6-month intervals. Testing HbA1c at a 1-month interval was more common in Wetaskiwin and Calgary. This short interval between HbA1c tests was unexpectedly high, and it is possible that unstable or new patients contributed to this peak but this cannot be deduced from this data set. All four regions had their highest frequency mode at 3 months, and the mode at 6 months was a discernible peak shoulder. Several authors have analyzed similar data to depict the extent of compliance

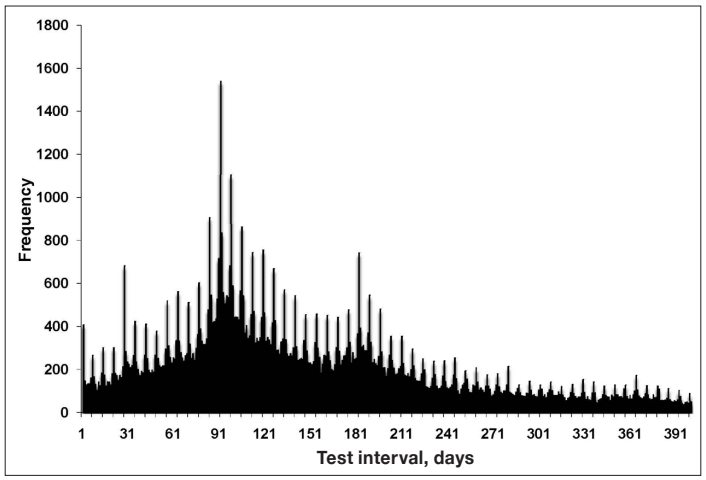

Figure 3. Frequency distribution of HbA1c test intervals in the Edmonton region.

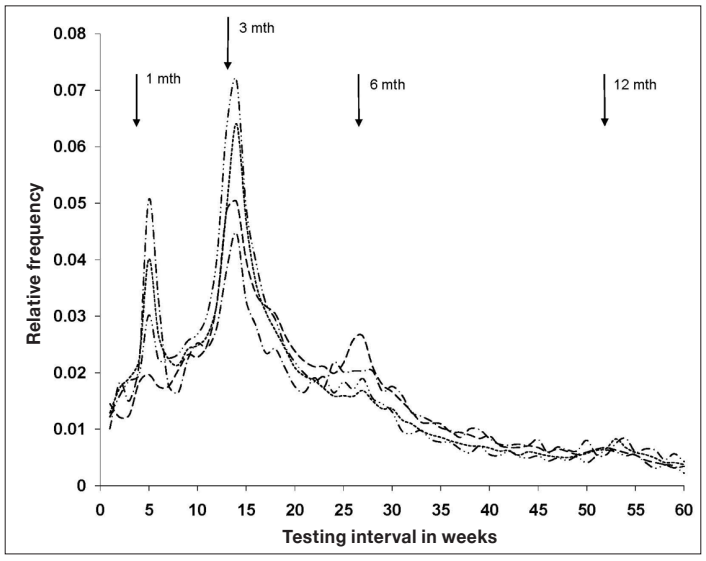

Figure 4. Relative frequency of HbA1c test intervals during the study period by region. •••, Calgary; – – –, Edmonton; -••-, Red Deer; -•-, Wetaskiwin.

with the ADA and CDA guidelines for the frequency of HbA1c testing by describing the extent that the testing interval was too short (<29 days, <1 month) or too long (>89 days, >3 months).[10,11] Data in **Figure 4** show that there was a clear attempt for a 3-month testing interval in each region, but in practice the testing occurred at 3 months ± 3 weeks. Applying the strict thresholds used by others to assess guideline compliance by physicians could yield misleading overestimation of the lack of guideline compliance by not accounting for the delay between physician visits and patients phlebotomy. In our opinion, data in **Figure 4** with the mode at 3 months depict partial compliance with the CDA guideline. In lieu of emphasizing numerical descriptors, we would point to the broad peaks and long tail to the right in **Figure 4**, which indicate that there is a great deal of inconsistency in the management of diabetes at this time in all four regions studied. If both physicians and patients adhered more rigidly to guidelines then a more uniform pattern around the 3-month mode would be observed.

Figure 5 depicts cumulative distribution plots for the intervals of HbA1c testing for each region. Similar sinusoidal curves for HbA1c have been reported previously in evaluation repeat laboratory testing intervals.[7,10] The sinusoidal shape of the cumulative curve is caused by the multimodal distribution of data (**Figure 4**). While the cumulative plot suggests that greater than 90% of patients with diabetes have HbA1c tests repeated within 1 year in all regions and that this is consistent with the ADA guideline, the plot masks the variation in shorter term testing intervals shown in **Figure 4**.

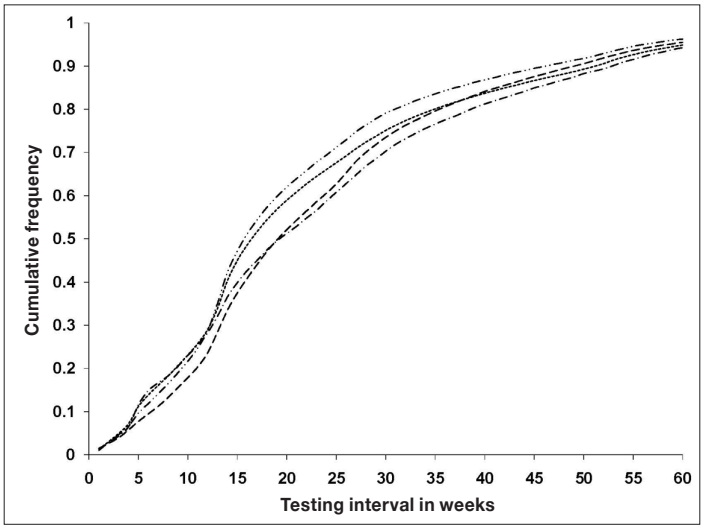

Figure 5. Cumulative frequency distribution of HbA1c testing intervals. ●●● , Calgary; – – – , Edmonton; -●●- , Red Deer; -●- , Wetaskiwin.

This analysis of the variation of HbA1c test use in four regions of Alberta has revealed similarities and notable differences. The suspicion that large numbers of nondiabetic patients were having infrequent HbA1c tests in all regions was confirmed; however, further study will be required to understand the disparity in testing nondiabetic patients in these regions. While there is no consensus among practice guidelines for the optimal frequency of HbA1c measurement in diabetic patients, both the ADA and the CDA guidelines suggest multiple measurements per year to assure that glycemic control is maintained. This study showed there are regional differences in the short-term HbA1c testing intervals and a consistent and detectable effort to achieve the 3-month testing interval suggested by the CDA. The broad multimodal frequency distributions and the long tails to the right in **Figure 4** suggest that all regions could improve the consistency in the testing practices, and responsibility for that lies with both physicians and patients. In the Edmonton region, a decision was made to limit repeat unnecessary HbA1c testing. The laboratory is canceling any HbA1c request that is ordered within 28 days of a previous analysis. The full impact of this restriction is not known at the time of writing.

Acknowledgement:

A preliminary report was presented at the annual meeting of the Canadian Society of Clinical Chemists.[12]

References:

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
2. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2005;28:S4-S36.
3. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabet. 2003;27 Suppl 2.
4. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab. 2008;93(7):2447-53.
5. Otto E, Higgins T, Toth E, Attrill J, Winchester T, Cembrowski GS. Non-optimal utilization of glycohemoglobin testing in Northcentral Alberta [abstract]. Can J Diabetes Care. 1999;23:87.
6. Tran DV, Cembrowski GS, Lee T, Higgins TN. Application of 3-D Delta check graphs to HbA1c quality control and HbA1c utilization. Am J Clin Pathol. 2008;130(2):292-8.
7. van Walraven C, Raymond M. Population-based study of repeat laboratory testing. Clin Chem. 2003;49(12):1997-2005.
8. Woodward G, van Walraven C, Hux JE. Utilization and outcomes of HbA1c testing: a population-based study. Can Med Assoc J. 2006;174(3):327-29.

9. Sanmartin C, Gilmore J. Diabetes-prevalence and care practices. Health Rep. 2008;19(3):59-63.

10. Akan P, Cimrin D, Ormen M, Kume T, Ozkaya A, Ergor G, Abacioglu H. The inappropriate use of HbA1c testing to monitor glycemia: is there evidence in laboratory data? J Eval Clin Pract. 2007;13(1):21-4.

11. Salvagno GL, Lippi G, Targher G, Montagnana M, Guidi GC. Monitoring glycaemic control: is there evidence for appropriate use of routine measurement of glycated haemoglobin? Clin Chem Lab Med. 2007;45(8):1065-7.

12. Wesenberg JC, Higgins TN, Cembrowski GS, Tran DV, Lyon AW. A tale of HbA1c utilization in four Alberta cities. Clin Biochem. 2008;41:1286.