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6.1.2.2 Quality Specifications for Haemoglobin A1c Assays in the Monitoring of Diabetes

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Analytical goals for the performance characteristics of assays of haemoglobin A1c (HbA_{1c}) have been investigated based on within-subject biological variation and on the clinical significance of a certain change in HbA_{1c} concentrations in the individual during monitoring of metabolic control. The derived goals are highly dependent on the assumptions made but, when several goals are to be considered, the most demanding should be used.

CLINICAL SITUATION

Measurements HbA_{1c} are used to monitor glycemic control in diabetes mellitus (1). A strong and curvilinear relation between HbA_{1c} and mean blood glucose concentration over the preceding 6-8 weeks has been demonstrated (2). Moreover, regular measurements of HbA_{1c} has been shown to lead to changes in diabetes treatment and improvement of metabolic control, indicated by a lowering of HbA_{1c} values (3). The objectives of monitoring glycated haemoglobin are to reach near-normal and steady concentrations. Consequently, clinical strategies have to be analyzed to generate goals for analytical quality.

CHARACTERISTICS OF THE METHOD

The present evaluation of quality specifications has been based on both clinical goals setting (4), biological variation data (5, 6) and theoretical goal setting (7). Data on biological variation are obtained from studies using an isoelectric focusing method for measurements of HbA_{1c} (4, 5).

MODELS FOR EVALUATION OF QUALITY SPECIFICATIONS

To define the clinical goals for analytical quality, it was important to understand the relationship between quality of performed analyses and medical needs (4). Clinicians have proposed that at a change of 1% HbA_{1c} in an individual (e.g. from 9.5% to 10.5%) should be considered a significant change in metabolic control and cause clinical attention. A change of 2% HbA_{1c} should make the physician intervene actively (5, 8, 9). Concerning the significance of a change in HbA_{1c} in the individual, the within-subject biological variation (CV_{Bw}) is determining and analytical imprecision become most demanding. The two concepts that provide the basis for the analytical goal-setting for tests used in monitoring such changes are:

a. The postulate of Harris (10) that analytical imprecision (CV_A) should be less than, or equal to, one-half the within-subject biological variation (CV_{Bw}), that is:

$$CV_A \leq 0.5 \cdot (CV_{Bw})$$

b. The proposal that analytical imprecision depends in the change (D) that it is desirable to detect clinically, the probability that such a change should exist, and the within-subject biological variation, according to the formula (11):

$$CV_A < [(D^2/2 \cdot z^2) - CV_{Bw}^2]^{1/2}$$

where z the z-statistic, which depend solely on the probability selected for significance.

EVALUATION OF QUALITY SPECIFICATIONS

a. We have previously estimated within-subject variation in insulin-dependent diabetics (5) and found CV_{Bw} = 4.1%. Using the postulate of Harris, the estimated goal for imprecision in the HbA_{1c} assay is thus: $CV_A \leq 0.5 \cdot 4.1 = 2.1\%$.

b. Attention to significant changes in HbA_{1c} concentrations should be drawn early, consequently the probability that a change in results of 1% HbA_{1c} (which is change of 10%) was set moderately low, at the 0.80 confidence level. From the above formula:

$$CV_A < [(10^2/2 \cdot 1.28^2) - 4.1^2]^{1/2}$$

$$\text{i.e. } CV_A < 3.7\%$$

A change of 2% HbA_{1c} in an individual (which is about a 20% change) would cause therapeutical intervention and the physician should be very confident that this change is

significant; the probability is therefore set at 0.99 and the analytical goal becomes CV_A <3.6%.

DISCUSSION

Goal setting cannot be static and must evolve with new knowledge and concepts. Clinical strategies should be analyzed in detail as the needs for analytical quality are different in various situations. We have previously evaluated analytical goals based on the criterion that HbA_{1c} concentrations should be below a certain level in patients with diabetes mellitus (12). Accepting this strategy makes analytical bias important.

The present evaluation of analytical goals is based on clinical significance of a certain change within the individual during monitoring of HbA_{1c}. Since monitoring is usually performed in a single laboratory, using one analytical method, the problem, of bias is somewhat irrelevant, whereas the within-subject biological variation is determining and analytical imprecision most demanding. We find it interesting that the goals in the two clinical monitoring situations were almost identical. Moreover, the goals derived by using this model were more stringent than those empirically proposed by an Expert Committee (13), namely CV_A less than five percent.

CONCLUSIONS

1. A number of different goals for analytical quality can be derived when different clinical situations using the same quantity are analyzed.
2. When the clinical situation is well defined, the use made of the result should be the basis for goal-setting; if this is unknown, data on biological variation should be the basis for the goal.
3. In monitoring of patients using results from the same laboratory - the analytical imprecision is the most important of the performance characteristics.
4. If several goals are considered to be applicable, the most demanding should be used.

REFERENCES

1. Singer, D.E., Coley, C.M., Samet, J.H. & Nathan, D.M. Tests of glycemia in diabetes mellitus. Ann Int Med 1989;110:125-37.

2. Svendsen, P.Aa., Lauritzen, T., Soegaard, U. & Nerup, J. Glycosylated haemoglobin and steady-state mean blood glucose concentration in type I (insulin-dependent) diabetes. Diabetologia 1982;23:403-5.
3. Larsen, M.L., Hørder, M. & Mogensen, E.F. Effect of long-term monitoring of glycosolated hemoglobin levels in insulin-dependent diabetes mellitus. N Eng J Med 1990;323:1021-5.
4. Larsen, M.L., Blaabjerg, O., Petersen, P.H., Hansen, H. & Høorder, M. Analytical goal setting prior to selection of a method for glycated haemoglobin. Scand J Clin Lab Invest 1990;50:715-21.
5. Petersen, P.H., Larsen, M.L. & Hørder, M. Prerequisites for the maintenance of a certain state of health by biochemical monitoring. In: Harris, E.K., Yasaka, T., eds. Maintaining a Healthy State within the Individual. Amsterdam; Elsevier 1987;147-58.
6. Fraser, C.G. The application of theoretical goals based on biological variation of proficiency testing. Arch Pathol Lab Med 1988;112:404-15.
7. Fraser, C.G. & Harris, E.K. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci 1989;27:404-37.
8. Walinder, O., Wibell, L. & Boström, H. The clinical value of HbA_{1c} determinations. Acta Med Scand 1980; suppl. 639:17-22.
9. Dunn, P.J., Cole, R.A., Soeldner, J.S. et al. Stability of hemoglobin A1c levels on repetitive determinations in diabetic outpatients. J Clin Endocrin Metab 1981;52:-1019-22.
10. Harris, E.K. Statistical principles underlying analytical goalsetting in clinical chemistry. Am J Clin Pathol 1979;72:374-82.
11. Fraser, C.G., Petersen, P.H. & Larsen, M.L. Setting analytical goals for random analytical error in specific monitoring situations. Clin Chem 1990;36:1625-28.
12. Petersen, P.H., Larsen, M.L. & Fraser, C.G. The quality needed for measuring glycated haemoglobin. An application. Upsala J Med Sci 1990;95:195-90.
13. National Diabetes Data Group: Report of the Expert Committee of Glycosylated Hemoglobin. Diabetes Care 1984;7:602-6.

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