Interpretation of Hemoglobin $A_{1c}$ (HbA$_{1c}$) Values among Diabetic Patients: Implications for Quality Specifications for HbA$_{1c}$

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Background: Few studies have examined patients’ views, knowledge, and understanding of glycohemoglobin $A_{1c}$ (HbA$_{1c}$) testing. We explored such issues in patients with type 1 diabetes and used their statements to estimate analytical quality specifications for HbA$_{1c}$ testing.

Methods: We recruited 201 patients from a hospital outpatient clinic. A questionnaire was used to collect information on diabetes characteristics, perceived knowledge of HbA$_{1c}$, last HbA$_{1c}$ value, HbA$_{1c}$ target value, and thresholds for action. Patients were asked to indicate the magnitude of change in HbA$_{1c}$ from 9.4% that they would consider to be a true (real) change; from their responses, we calculated patient-derived quality specifications for HbA$_{1c}$.

Results: Fifty-eight percent of the patients felt they had “high” knowledge about HbA$_{1c}$, and >80% of respondents knew their last HbA$_{1c}$ value, their target HbA$_{1c}$, and the threshold value of HbA$_{1c}$ for treatment intensification. The mean acceptable HbA$_{1c}$ value was 7.5%. Patients with lower values on their most recent tests reported lower target values for HbA$_{1c}$ and lower values for the upper HbA$_{1c}$ threshold for treatment intensification. An analytical CV (CV$_a$) of 3.1% would be satisfactory for 75% of patients when HbA$_{1c}$ is increasing (80% confidence), and a CV$_a$ of 3.2% would be satisfactory for 75% when HbA$_{1c}$ is decreasing (95% confidence).

Conclusions: Type 1 patients’ perceived knowledge about HbA$_{1c}$ testing is high. They are well informed about their own personal results and about target values and the upper HbA$_{1c}$ threshold for action. The patient-derived analytical quality specification for imprecision (CV) is 3.1%.

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The relationships between glycohemoglobin A1c (HbA$_{1c}$) and blood glucose concentrations and late complications have been established over the last 30 years (1–7). HbA$_{1c}$ measurements have become routine practice, and it has been shown that long-term regular measurement of HbA$_{1c}$ leads to improved metabolic control (8).

In a previous study, we examined the use and interpretation of results from glucose self-measurements among diabetic patients (9, 10). A similar study of HbA$_{1c}$ would be more complicated because the patients do not perform the analysis themselves. Nonetheless, because HbA$_{1c}$ has become the most important way of measuring long-term metabolic control, diabetes caregivers and patients need a similar understanding and interpretation of HbA$_{1c}$ values and what should be considered “real” changes in HbA$_{1c}$. Today, patients’ knowledge about diabetes and HbA$_{1c}$ comes not only from caregivers, but increasingly from other sources such as diabetes associations, diabetes magazines, and sites on the World Wide Web. The use and interpretation of HbA$_{1c}$ results among physicians (II, 12) have been studied, but there is a lack of studies of patients’ views, knowledge, and understanding of HbA$_{1c}$ testing. Consequently, this study was designed to explore these aspects among type 1 diabetes patients and to use their statements concerning changes in HbA$_{1c}$ to define patient-derived analytical quality specifications for the HbA$_{1c}$ analysis.

Materials and Methods

Patients with type 1 diabetes mellitus were recruited from March to November 1998. Consecutive individuals were included at their scheduled follow-up visit with an endo-
In our clinic, like most clinics for diabetic patients, virtually every patient with type 1 diabetes performs self-monitoring of blood glucose (SMBG). All follow-up visits usually include a HbA1c measurement performed in the hospital central laboratory, where the upper reference limit for HbA1c is 5.9%. HbA1c is measured on a Diamat HPLC (Bio-Rad Laboratories), and the values obtained are traceable to the “DCCT method”. Performance is controlled by internal quality controls as well as by participation in an external quality control scheme where the target values are determined with the DCCT method. Most of the studied patients attend the clinic as their primary location for diabetes care. Over the past 10 years, it has been a clinical practice goal to measure HbA1c every 3 months and to inform patients about the results, as recommended by the American Diabetes Association (13).

Generally, newly diagnosed patients in Norway are, as in our clinic, informed and educated about what HbA1c is and what the short- and long-term consequences of different degrees of metabolic control might be. On the basis of established recommendations, it is the policy to discuss and to set individual HbA1c targets together with the patient (7,13,14).

The present study is based on self-reported data obtained with a questionnaire developed in cooperation with a diabetes specialist, diabetes nurses, and patients with type 1 diabetes. The questionnaire was evaluated by 10 type 1 patients in a pilot study before recruitment for the larger study was initiated, and only minimal changes were made. Assisting personnel handed the questionnaire to the patients when they arrived; patients answered the questions without assistance or professional influence before consultation with the nurse/doctor. Responders sealed their questionnaires in envelopes and placed them in a box, but because the questionnaires were anonymous, routines were established to ensure that no patient was included more than once.

In the general part of the questionnaire, patients stated their age, sex, and year that their diabetes was diagnosed as well as how long and how frequently they had performed SMBG. We then assessed patients’ perceived general knowledge about the HbA1c test, whether they knew their last HbA1c result, their target HbA1c value, and the upper and lower thresholds for treatment changes (Fig. 1). The questionnaire included an opportunity to respond “Don’t remember” or “Don’t know” to these questions, which probably increased the likelihood of true and correct responses.

The two last questions assessed the magnitude of change in HbA1c from 9.4% necessary for patient to be certain that the change indicated a true (real) improvement or deterioration of their diabetes, i.e., the so-called critical difference (CD). The 9.4% value was chosen based on experience from a comparable study and our pilot test, both of which indicated that patients felt that they could foresee both improvement and deterioration of their metabolic control when this value was used as baseline (12).

Regarding the HbA1c test that is performed at your follow-up visits:

1. How good is your knowledge of the HbA1c test and its meaning for a person with diabetes?
   - Very good knowledge: ☐
   - Sufficient knowledge: ☐
   - Some knowledge: ☐
   - Little knowledge: ☐
   - No knowledge: ☐

2. Do you remember the result of your last HbA1c test?
   - About ___% Don’t remember: ☐

3. Indicate the value that you would consider satisfactory for your HbA1c? ___% DON'T KNOW: ☐

4. Indicate how high your last HbA1c should be before you mean that changes should be made in your diabetes treatment? ___% DON'T KNOW: ☐

5. Indicate how low your last HbA1c should be before you mean that changes should be made in your diabetes treatment? ___% DON'T KNOW: ☐

Imagine that your last HbA1c result was 9.4%. With this value as starting point:

6. To what value will your HbA1c have to decrease to for you to be sure that it represents a true improvement in your diabetes treatment? ___% DON'T KNOW: ☐

7. To what value will your HbA1c have to increase for you to be sure that it represents a true deterioration in your diabetes treatment? ___% DON'T KNOW: ☐

The CD is conventionally defined as the difference needed between two consecutive test values to be certain (with a given probability) that the two results actually are different (i.e., that the change is not caused by analytical and biological variation). The formula used is: CD = bias + z value × √CV a 2 + CV i 2. We used z values for one-sided tests and 95% or 80% probabilities (z values of 1.64 and 0.84, respectively) to reflect the participants’ certainty before initiating an action. CV a is an estimate of the analytical imprecision (16), and CV i is the mean within-subject CV for HbA1c (16). Calculations were performed using this formula with a CVi of 4% (17). Patients’ responses concerning the magnitude of change in HbA1c from 9.4% that they considered to be a true (real) change were taken as the CD. We then rearranged the formula to calculate the CV a, which can be considered the quality goal for imprecision, assuming the bias component to be zero (9,12,18).

The Student t-test or nonparametric tests were used when appropriate. Correlation coefficients were calculated using the Pearson method. Statistical significance was set at 5%.

Results
A total of 201 patients with type 1 diabetes were enrolled in the study, and none refused to participate. Most
patients had been diagnosed with diabetes >14 years prior to the study. Patient characteristics are given in Table 1. Six patients performed SMBG less than once per week (SMBG frequency = 0), and seven patients were diagnosed with diabetes and had initiated SMBG within the last year (diabetes and SMBG duration = 0). The women were older with longer duration of diabetes and performed SMBG more frequently than the men (P <0.05). For all other questions on the questionnaire, no differences were seen in responses between men and women, and thus combined results are presented.

Question 1 assessed patients’ perceived knowledge about HbA1c testing (Fig. 1). Fifty-eight percent responded that they had “high” knowledge of HbA1c testing [categories “very good” (18%) or “sufficient” (40%)], whereas 42% thought they had “low” knowledge [categories “some” (30%), “little” (10%), or “no” (2%)]. The two groups did not differ with regard to age, sex, or SMBG frequency. Patients in the high-knowledge group had a longer duration of diabetes (16.2 vs 12.7 years; P = 0.025) and had performed SMBG longer (10.8 vs 8.6 years; P = 0.012) than those in the low-knowledge group.

Questions 2–5 assessed personal HbA1c values, target values, and thresholds for action (Table 2). Response rates were lower on these questions, varying from 70% on question 5 to 90% on question 3. Five percent of patients responded that they did not know their own HbA1c target (question 3), whereas 18% reported that they did not know their lower HbA1c threshold for action (question 5). Patients who had a low HbA1c value at their last visit also reported lower HbA1c satisfactory values (r = 0.436; P <0.01) and lower upper thresholds for treatment intensification (r = 0.631; P <0.01). There was no significant difference in responses concerning HbA1c values on these four questions between the two groups with different knowledge levels, but patients in the low-knowledge group had significantly lower response rates on these four questions compared with the high-knowledge group (mean, 72% vs 90%; P <0.05).

The magnitude of change in HbA1c from 9.4% that patients considered a true change reflects the difference a HbA1c method should be able to detect, and thus the patient-derived CD for HbA1c. The calculated CVa values based on these CDs at the 80% and 95% confidence levels are shown in Table 3. The results show that the responders have higher quality expectations when HbA1c is increasing compared with decreasing from 9.4%. Approximately one-half of the patients indicated that for increasing HbA1c (80% confidence), the resulting CVa should be <3.1%, assuming a bias of 0%. The values were not significantly different for the two knowledge groups, but the response rates were significantly lower on questions 6 and 7 for the low-knowledge group compared with the high-knowledge group (67% and 58% vs 90% and 79%, respectively; P <0.01).

Discussion

The patients in our study were experienced in SMBG, with a mean time since diagnosis of 14.7 years. They were recruited consecutively and represent a cross-sectional

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### Table 1. Patient characteristics (n = 201).a

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
<th>Mean difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>31.8 (16–77)</td>
<td>30.2 (16–52)</td>
<td>33.3 (17–77)</td>
<td>3.1 (0.01–6.2)</td>
<td>0.049</td>
</tr>
<tr>
<td>Years with diabetes mellitus</td>
<td>14.7 (0–50)</td>
<td>12.6 (0–34)</td>
<td>16.6 (0–50)</td>
<td>4.0 (1.0–6.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Years performing SMBG</td>
<td>10.0 (0–27)</td>
<td>9.2 (0–20)</td>
<td>10.7 (0–27)</td>
<td>1.5 (–0.2–3.2)</td>
<td>0.084</td>
</tr>
<tr>
<td>Frequency of SMBG, no. of measurements/week</td>
<td>11.2 (0–65)</td>
<td>9.5 (0–40)</td>
<td>12.8 (0–65)</td>
<td>3.4 (0.6–6.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

a Other than sex, data are mean (range).

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### Table 2. Patient responses to different questions concerning HbA1c.

<table>
<thead>
<tr>
<th>Questionsa</th>
<th>HbA1c value, %</th>
<th>Mean ± SD</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Result of last HbA1c test (n = 166)</td>
<td>8.4 ± 1.5</td>
<td>7.5</td>
<td>8.1</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>3. Satisfactory HbA1c value (n = 181)</td>
<td>7.5 ± 0.9</td>
<td>7.0</td>
<td>7.5</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>4. Upper HbA1c threshold to indicate a need for treatment changes (n = 175)</td>
<td>9.5 ± 1.6</td>
<td>8.5</td>
<td>9.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>5. Lower HbA1c threshold to indicate a need for treatment changes (n = 141)</td>
<td>5.5 ± 1.1</td>
<td>5.0</td>
<td>5.5</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

a Numbers refer to questions in Fig. 1.
sample of our clinic’s diabetes population; we have no reason to believe that they are different from other type 1 patients in Norway. The patients studied performed SMBG a mean of 11 times/week, which is lower than recommended by the American Diabetes Association (13), but the relationship between frequency of SMBG and long-term outcome is not well established. Like most diabetes patients, they have, over the years, become more knowledgeable about HbA1c and their diabetes through educational efforts of their caregivers and, increasingly, from other sources of information. Our general question regarding knowledge level was designed to get a simple expression of perceived patient knowledge about HbA1c. A higher percentage of the more experienced patients (longer diabetes duration and SMBG performance) were in the high-knowledge group, which may be explained by their accumulation of knowledge over the years. The patients who had performed SMBG for the longest period of time tended to be more knowledgeable. We did not find associations between perceived knowledge and the HbA1c targets and thresholds stated. Several authors point to this as a more complex relationship and emphasize that knowledge, attitude, and motivation are most important for patients’ ability to take therapeutic actions to maintain or improve their HbA1c values (19–23). However, we did find a significantly lower response rate on all HbA1c questions for the low-knowledge compared with the high-knowledge group, indicating that the former group found the questions more difficult. On the other hand, even if the nonresponders hypothetically had responded identically to the rest of the low-knowledge group, the mean differences in responses between the low-and high-knowledge groups would not have reached statistical significance.

More than 80% of the studied subjects knew their last HbA1c value, and 90% responded to the crucial question on what a satisfactory HbA1c value should be. The median HbA1c target value was 7.5%, and 75% of the patients declared their target to be ≤8%. This is in line with international recommendations giving a HbA1c target value of 7.0–7.5% (7, 13, 24). Thirteen of 181 patients (7%) gave target values of ≥9%, which may be reasonable for patients having difficulty in controlling their blood glucose.

At an HbA1c value of 10% (Table 2, question 4), 25% of the patients still did not state that treatment intensification should occur. This might reflect that for some patients, the disease is more difficult to control and that targets, therefore, are individualized rather than based directly on recommended values. The fact that only 25% of patients felt that 6% HbA1c is too low (Table 2, question 5), might indicate that many patients have not experienced or are unaware of the serious problems associated with the frequent and sometimes severe hypoglycemia that occurs when HbA1c decreases to this concentration (7). This is underscored by the finding that ~25% of the patients indicated that therapeutic actions (less-intense therapy) can be postponed at a HbA1c value of 5.0%. The well-controlled patients set lower targets and adjusted their therapy on lower HbA1c concentrations.

On questions 6 and 7, we asked for CDs set by the patients when estimating true changes in HbA1c from 9.4%. The 20–30% who did not respond to these questions probably were unable to judge this issue of CD. The responding patients set lower CDs when HbA1c increased than when it decreased (medians, 0.6% vs 1.4%). In a similar study, general practitioners gave corresponding median CDs of 0.6% and 1.0%, respectively, when asked which changes in HbA1c that they considered true in response to a case history (12). General practitioners

![Fig. 2. Minimal changes in HbA1c values (CDs) indicated by type 1 diabetes patients and general practitioners (GPs) (12) to signify improvement or deterioration of metabolic control, given as percentage of increase or decrease. Some symbols refer to two or more identical observations. See text for further explanation.](image-url)
overall seemed to have higher quality expectations for the HbA\textsubscript{1c} analysis compared with the type 1 diabetes patients. This similarity in response patterns from 407 general practitioners and 201 type 1 patients, i.e., higher CDs when HbA\textsubscript{1c} increases than when it decreases, is shown in Fig. 2. The same response pattern was found in a study involving family practitioners, internists, and endocrinologists (11). We believe that this finding is attributable to the adverse effect of poorer metabolic control compared with an improvement; consequently, both doctors and patients want to detect smaller “increases” than “decreases” when judging HbA\textsubscript{1c} results, probably to initiate therapeutic actions. This might imply that both patients and doctors will intensify treatment with <95% confidence that the increase in HbA\textsubscript{1c} is true, but want to be more confident that a decrease in HbA\textsubscript{1c} in fact has occurred before making treatment changes. To reflect the optimum quality (18) stated by the patients in this study, a CV\textsubscript{a} of 3.1% would be satisfactory for 75% of patients when HbA\textsubscript{1c} is increasing (80% confidence), whereas a CV\textsubscript{a} of 3.2% would be satisfactory for 75% when HbA\textsubscript{1c} is decreasing (95% confidence; Table 3).

Similarly, to establish analytical quality specifications for HbA\textsubscript{1c}, Larsen (25) stated that the test should be able to detect a true change in HbA\textsubscript{1c} of >1% (e.g., change in HbA\textsubscript{1c} from 7% to 8%). In this example, bias should be negligible, specificity should exclude other minor hemoglobin, and the test should be able to measure the lowest occurring HbA\textsubscript{1c} in healthy individuals. This approach thus would establish CV\textsubscript{a} goals of 2–4%. This method was described as a way of defining analytical goals for clinical practice but could also be applicable to patients who have agreed on their treatment goals and targets with their doctors. Kolatkar et al. (11) examined changes in HbA\textsubscript{1c} interpreted by family practitioners, internists, and endocrinologists and found an optimum CV for HbA\textsubscript{1c} of 2–4%, not taking bias into account.

From the literature and external national quality-control surveys, we know that the most common analytical methods for HbA\textsubscript{1c} have a CV\textsubscript{a} of ~3% (12, 26–28). In the setting of diabetes follow-up, testing of HbA\textsubscript{1c} typically takes place at intervals of at least 2 or more months. Bias (systematic error of measurement) is a more important part of total analytical error when the time interval between tests is long or different laboratories or lot numbers of reagents are used (16, 29). Including a bias component will put higher demands on patient-derived analytical quality specifications for imprecision (CV) in this setting. When patients and their caregivers set clinical treatment goals, including HbA\textsubscript{1c} targets, knowledge about analytical quality can be crucial (29, 30), and analytical imprecision will probably be considered most important in the monitoring situation (16).

In conclusion, most of the studied type 1 diabetes patients were aware of their last HbA\textsubscript{1c} result, and they had relatively high perceived knowledge about HbA\textsubscript{1c} testing. Well-controlled patients seem to have higher ambitions and therefore set lower targets and act on lower thresholds. Patients apparently act on smaller increases in HbA\textsubscript{1c} than decreases. These findings correspond with the patterns found for doctors’ use and interpretation of HbA\textsubscript{1c} values. The patient-derived quality specification for imprecision (CV) is ~3%.

References


