Glycohemoglobin: A Primary Predictor of the Development or Reversal of Complications of Diabetes Mellitus

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Background: Diabetes mellitus is a major health problem worldwide with long-term micro- and macrovascular complications responsible for a majority of its morbidity and mortality. The development and progression of these complications relate strongly to glycemic control.

Methods: We reviewed the literature extensively for studies that relate glycemic control to the development and progression of diabetic complications. We discuss the problems of standardizing glycohemoglobin measurements for monitoring diabetic therapy and also consider recently developed electrospray ionization mass spectrometry methods that have been considered as candidate reference methods for estimation of glycohemoglobin.

Results: Several clinical trials and studies have clearly shown that improved glycemic control is strongly associated with decreased development and/or progression of complications in both type 1 and type 2 diabetes mellitus. Irrespective of the methods used for estimating glycohemoglobin, these results underline the importance of glycohemoglobin for guiding therapy of diabetes mellitus. Recently developed candidate reference methods promise to yield greatly improved standardization for the measurement of glycohemoglobin.

Conclusions: Glycohemoglobin measurement remains the optimal indicator of glycemic control in diabetic patients, but translation of findings from clinical trials to clinical practice worldwide demands consistent values across all assays. To ensure that the important prognostic information still applies to all diabetic patients with the application of the reference method(s), the hemoglobin A1c values reported in the major clinical trials will have to be translated into statistically and computationally compatible values based on the new reference system(s).

Epidemiology of Diabetes Mellitus

Over the past several decades, diabetes mellitus has become a major health problem worldwide, reaching epidemic proportions in many developing countries as well as in minority groups in the developed world (1, 2). In the United States, the prevalence of diabetes diagnosed in people 20–74 years of age increased from 4.9% in 1990 to 6.5% in 1998 (3). Worldwide projections suggest that >220 million people will have diabetes by the year 2010, and the majority of these (~213 million) will have type 2 diabetes (4). In 1997, healthcare costs related to diabetes in the US were ~$100 billion, with one-half in direct costs; these costs also are projected to rise considerably (5).

Type 1 diabetes is accompanied by long-term micro- and macrovascular complications, the primary causes of morbidity and mortality in these patients. Diabetic nephropathy, as the single most common cause of end-stage renal disease, accounts for more than one-third of all cases. Type 2 diabetes mellitus is associated with increased cardiovascular and overall mortality. In fact, type 2 diabetic patients diagnosed before 70 years of age have only 70% of the life expectancy of nondiabetic people (6, 7). Epidemiological data suggest that classic cardiovascular risk factors, such as hypercholesterolemia, hypertension, and smoking, do not account for the excess risk of cardiovascular morbidity and mortality in type 2 diabetes mellitus. Thus, understanding the pathogenesis and preventing and/or ameliorating these long-term complications have been major goals of research in diabetes mellitus.

Nonenzymatic Glycation

Of the several pathogenic mechanisms by which hyperglycemia may lead to altered tissue structure and function, nonenzymatic glycation (encompassing the attachment of the free aldehyde groups of glucose or other
sugars to the nonprotonated free amino groups of proteins) changes the structure and function of several soluble and insoluble proteins in vivo and in vitro (8–13). Because cells and their extracellular matrix share a dynamic and reciprocal relationship (14), modulations of matrix components by glycation leads to altered cell behavior, including changes in cell spreading, phosphorylation of key intracellular signaling molecules, and expression of extracellular matrix proteins and their modulators (15–17). Extracellular matrix from diabetic patients is more extensively glycated than extracellular matrix from nondiabetic people. In addition, the accumulation of glycation products and the accompanying structural extracellular matrix modifications correlate with the development of functional complications of diabetes (18–21). These changes in tissue structure and function are slow and cumulative, producing a long time lag between the start of diabetes and the onset and progression of the complications.

**Glycohemoglobin**

Hemoglobin is one of many proteins that undergo nonenzymatic glycation, and glycohemoglobin (GHB) is a general term for hemoglobin nonenzymatically glycated by glucose. Rahbar (22) first described GHBs in 1968 as diabetic hemoglobins. Potential glycation sites of the hemoglobin A molecule include the N-terminal amino acid valine of the four-polypeptide chains and all of the free ε-amino groups of lysine residues. The predominant glycation site is the N-terminal valine residue of the β chain, which accounts for ~60% of bound glucose. Total GHB refers to all GHB species that are measured by affinity chromatographic methods (23). Hemoglobin A₁ (HbA₁), which is more negatively charged than HbA, may be detected by cation-exchange chromatography and includes HbA₁a, HbA₁b, and HbA₁c, which are named in order of their elution from the column. Of these, HbA₁c represents the most prevalent glycated species and is defined by the IFCC as HbA irreversibly glycated at one or both N-terminal valines of the β chains. To a lesser extent, other glucose molecules are bound to 1 or more of the 44 glycation sites at the ε-amino groups within the hemoglobin molecule or at the N-terminal valines of the α chains (24, 25).

Because erythrocytes are freely permeable to glucose, the rate of formation of GHB is directly proportional to the ambient glucose concentration in which the erythrocyte circulates and to the duration of exposure. In addition, because the postsynthetic modifications of HbA irreversibly form GHB, the GHB concentration constitutes a reliable, integrated measure of the average blood glucose concentration over the life spans of circulating red cells (i.e., 2–3 months). Clinical GHB testing became widely available in the early 1980s, and thus objective measurement of long-term glycemic status became possible (26–29).

Measurement of GHB, either as HbA₁c or as total GHB, is widely used in clinical practice to monitor glycemia in diabetic patients. The American Diabetes Association (ADA) recommends GHB testing at least twice a year in patients who have stable glycemic control and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycemic goals. The ADA recommends that the goal of therapy should be a GHB concentration <7% and that treatment regimens should be reevaluated if GHB values are consistently >8%; these values apply only to assay methods that are certified as traceable to the Diabetes Control and Complications Trial (DCCT) reference method (30–32). GHB serves as a key predictor of the risk of developing diabetic complications. In addition, knowledge of GHB concentrations appears to alter the behavior of healthcare providers and/or patients, in turn improving glycemia and lowering GHB values (33).

**Glycohemoglobin and Diabetic Complications**

Only in the last decade have the DCCT (32) and the United Kingdom Prospective Diabetes Study (UKPDS) (34) clearly demonstrated that improved glycemic control reduces the development and progression of several micro- and macrovascular complications in both type 1 and type 2 diabetes mellitus. Interestingly, both studies used the same ion-exchange method (Bio-Rad Diamat HPLC). The key findings from these and other selected studies on several complications are summarized in the following sections and Tables 1–4. Figs. 1 and 2 represent the major findings of the DCCT, UKPDS, and Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESTDR) because each of these three major studies enrolled 3–4 times as many subjects as all of the other studies combined.

**RETINOPATHY (TABLE 1; FIGS. 1 AND 2)**

In the DCCT, which included 1441 type 1 diabetic participants, the mean HbA₁c in the groups receiving intensive therapy was 7.2%, which reduced the risk of developing retinopathy in the primary prevention cohort by 76% and reduced the risk of progression of retinopathy in the secondary intervention cohort by 54%, compared with the conventionally treated group (mean HbA₁c, 9.1%) (32, 35). In the UKPDS, 3867 newly diagnosed type 2 diabetic patients were followed over 10 years. Compared with the conventional group [average HbA₁c, 7.9% (6.9–8.8%)], the intensively treated group [with a lower average HbA₁c of 7.0% (6.2–8.2%)] had a 25% risk reduction for microvascular complications, including the need for retinal photo-

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1 Nonstandard abbreviations: GHB, glycohemoglobin; HbA₁c, hemoglobin A₁c; ADA, American Diabetes Association; DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study; WESTDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; SDIS, Stockholm Diabetes Intervention Study; EDIC, Epidemiology of Diabetes Interventions and Complications Study; EPIC, European Prospective Investigation of Cancer and Nutrition; NGSP, National Glycohemoglobin Standardization Program; and ESI-MS, electrospray ionization mass spectrometry.
coagulation (34). Of 102 type 1 diabetic patients in the Stockholm Diabetes Intervention Study (SDIS) followed for 7.5 years, 27% of patients receiving intensive therapy (mean GHb, 7.1%) developed serious retinopathy compared with 52% of patients receiving conventional treatment (mean GHb, 8.5%) (36). In WESTDR, with 1210 younger onset and 1780 older onset diabetic patients, HbA1c at baseline was a significant predictor of incidence and progression of proliferative retinopathy after adjustment for duration of diabetes (37, 38). HbA1c concentrations (divided into both quartiles and deciles) correlated with a consistent increase in retinopathy from the lowest (5.4–8.5%) to highest quartile (11.6–20.8%) and lowest to highest decile with no evidence of a threshold effect. Furthermore, the WESTDR investigators estimated that a 1.5% decrease in HbA1c would lead to a 24–33% decrease in the 10-year incidence of proliferative retinopathy. Wu et al. (39), who studied 137 type 2 diabetic patients for 5 years, found a 1.5-fold increased risk of retinopathy in patients with a high HbA1c of 10.5% compared with patients with a lower HbA1c of 6.9%. Henricsson et al. (40) studied 72 patients and demonstrated that each percentage increase in HbA1c was associated with a 1.56- to 1.68-fold increased risk of retinopathy. These and other studies (32, 34–42) are summarized in Table 1.

Nephropathy (Table 2; Figs. 1 and 2)
In the DCCT with the two cohorts combined, intensive therapy reduced the incidence of microalbuminuria (urinary albumin excretion ≥40 mg/24 h) by 39% and clinical grade albuminuria (urinary albumin excretion ≥300 mg/24 h) by 54% (32, 43). In the UKPDS, intensive therapy was associated with a reduction in progression of albuminuria and a 67% risk reduction in the proportion of patients having a twofold increase in plasma creatinine (34). Similar findings were found in the SDIS, with the difference in proportions between intensive and standard treatment being 16% (36). In the Wisconsin cohort, followed by Klein (38) over a period of 10 years, 28% of all younger and 36% of all older patients developed gross proteinuria, and 7% of all younger and 2% of all older patients developed renal failure. In that study (38), compared with patients in the lowest quartile, patients in the highest quartile of HbA1c had a two- to fourfold increased risk of both proteinuria and renal failure. In a recent study by Ravid et al. in 1998 (44), in which the authors followed 574 patients for 2–9 years, the risk of progression from microalbuminuria to macroalbuminuria was 18-fold greater in high vs low GHb groups. Tanaka et al. (45), who studied 123 type 2 diabetic patients, found that the group that developed microalbuminuria showed a higher 6-year mean HbA1c of 9.0% than the group that remained normoalbuminuric (8.1%). The HbA1c concentration separating normo- from microalbuminuric patients was 8.5%. These and other studies (32, 34, 36, 38, 43–46) are summarized in Table 2.

MACROVASCULAR DISEASE/OVERALL MORTALITY (Table 3)
In the DCCT, intensive therapy reduced, although not significantly, the risk of macrovascular disease by 41%, from 0.8 events to 0.5 events per 100 patient-years (32). In the UKPDS, the intensively treated group had a 10% lower risk for any diabetes-related death (P = 0.34) and 6% lower risk for all-cause mortality (P = 0.44) compared with the conventionally treated group; however, these differences were not statistically significant (34). In the Wisconsin cohort studied by Klein (38), the hazard ratio for dying was 1.9-fold greater for patients in the fourth quartile of HbA1c concentrations, relative to the first quartile. Similarly, Ravid et al. (44) found that a high GHb was associated with a 15-fold greater risk of cardiovascular morbidity and mortality compared with low values. As recently reported in the Norfolk cohort of the Euro-

Fig. 1. Mean HbA1c or HbA1 values in the DCCT (32), UKPDS (34), and WESTDR (38).

The decrease in mean HbA1c with intensive therapy or difference of mean GHb concentrations between the lowest and highest quartile was statistically significant: ¶, P <0.001; *, P <0.001. INT, intensive therapy; CONV, conventional therapy; pts, patients.

Fig. 2. Percentage of risk reduction for retinopathy and nephropathy after intensive therapy in the DCCT (32) and UKPDS (34), or in patients with GHb concentrations in the lowest quartile in the WESTDR compared with the highest quartile (38). The risk reduction was statistically significant: *, P <0.04; **, P <0.002; §, P <0.0031; ¶, P <0.0001.
Prospective Investigation of Cancer and Nutrition (EPIC), men with known diabetes clearly had increased mortality from all causes, from cardiovascular disease, and from ischemic disease (relative risks, 2.2, 3.3, and 4.2, respectively; \( P < 0.001 \) independent of age and other risk factors) (47). HbA1c concentrations at baseline were a strong predictor of cardiovascular risk factors, cardiovascular events, stroke, and overall mortality in these and other studies (32, 34, 38, 39, 44–52), as summarized in Table 3.

### Hypoglycemia

Although better glycemic control is clearly associated with decreased risk of development of diabetic complications, hypoglycemia is the major limiting factor for intensive therapy in all diabetic patients (both type 1 and type 2). In the DCCT and the UKPDS, the intensive treatment groups had a higher risk of hypoglycemia (32, 34). However, the DCCT Research Group also demonstrated significant benefits of sustaining \( \beta \)-cell function with intensive treatment and thereby significantly reducing the risk of severe hypoglycemia (53). In short, the benefits of intensive therapy must always be weighed against the greater risk of hypoglycemia.

### Reversal of Diabetic Complications

Diabetic complications develop insidiously and are difficult to reverse. Although rapid reversal of early renal lesions (e.g., mesangial expansion) has been demonstrated within months in diabetic rats rendered normoglycemic by islet or whole pancreas transplantation (54, 55), 5 years of normoglycemia with successful pancreas transplantation did not reverse established diabetic glomerular lesions in type 1 patients with their own kidneys (56). Only after 10 years of normoglycemia in these same pancreas transplant recipients were glomerular and tubular lesions ameliorated, i.e., a reduction in the thickness of the glomerular and tubular basement membranes and diminished mesangial matrix volume were achieved (57). Thus, even advanced lesions of diabetic nephropathy may be reversed, but only over a period of time (1 decade) approaching the duration of diabetes necessary to develop nephropathic lesions (1–2 decades) (20).

### Benefits of Improved Glycemic Control

All observations reviewed in this report clearly demonstrate the importance of improved glycemic control in preventing, delaying, or reversing complications in both diabetic patients.
Additional Uses of Glycohemoglobin

Increased GHb has been demonstrated to be a marker for cardiovascular risk factors, events, and mortality even in nondiabetic subjects (Table 4) (62–64). The Norfolk cohort of EPIC clearly demonstrated an increasing risk of macrovascular disease with increasing HbA1c in the non diabetic segment of the population (47). In addition, recently Ko et al. (65) showed that for diagnosing diabetes, the combine use of fasting plasma glucose and HbA1c obviated ~80% of oral glucose tolerance tests. With optimal standardization of GHb measurements, these results suggest that the measurement of GHb could potentially replace the oral glucose tolerance test as the screening and diagnostic test for diabetes mellitus. If the EPIC results (47) have broad application, GHb may be used as an additional risk factor in both diabetic patients and nondiabetic people.

Challenges Concerning the Measurement of Glycohemoglobin

Despite the overwhelming evidence that GHb measurements should be used to guide the therapy of diabetes, the test may be underutilized clinically. The ADA recommends measuring HbA1c at least twice a year in diabetic patients with stable glycemic control and more frequently in patients who are not meeting glycemic goals (31). In addition, although the ADA Provider Recognition Program iterates specific goals for HbA1c in the ambulatory population ~25% of diabetic patients may fail to have GHb determinations completed even annually (66).

One major challenge in implementing these standards has been the multitude of analytical methods for GHb (>20), most of which measure different combinations of chemically modified hemoglobins. The National Glycohemoglobin Standardization Program (NGSP) and an IFCC working group have continuously improved the standardization of GHb measurements to ensure that all methods measuring GHb are comparable to the results from the DCCT. For example, more manufacturers pro-
duce assays that have been certified by the NGSP as traceable to the DCCT reference method (67). In the United States, recent College of American Pathologist surveys show that 95% of laboratories report HbA1c and 5% report total GHb or HbA1. Overall, ~90% of the assay methods in the United States are NGSP certified. The ADA and the Health Care Financing Agency are working together in setting and trying to achieve therapeutic goals in the community (31). When specific numbers are set as goals for healthcare providers, standardization becomes even more critical. Although the procedure used in the DCCT has been proposed as the comparison method against which most assays should be standardized, there is no universally accepted reference method. For example, the HbA1c result by ion-exchange HPLC reflects only 60% specificity because of β-N-deoxyfructosyl-Hb; i.e., Hb glycated at the NH2 terminus of the β chain (68). Despite the challenges with GHb standardization, the studies reviewed here, irrespective of the different analytical methods used and the variation in the values for a “normoglycemic” reference population, clearly showed that poorer metabolic control was associated with an increased risk of micro- and macrovascular complications of diabetes mellitus.

### Recent Advances in Estimation of Glycohemoglobin

Recently, procedures using electrospray ionization mass spectrometry (ESI-MS) have been developed as candidate

<table>
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<tr>
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<tr>
<td>DCCT (32)</td>
<td>1441</td>
<td>6.5</td>
<td>INT therapy reduced the risk of macrovascular disease by 41%, although not significantly, from 0.8 to 0.5 events per 100 patient-years (mean HbA1c, 7.2% vs 9.1%)</td>
<td>Ion-exchange</td>
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<td>UKPDS (34)</td>
<td>3867</td>
<td>10</td>
<td>INT therapy group had a 10% lower risk for any diabetes-related death (P = 0.34) and 6% lower risk for all-cause mortality (P = 0.44)</td>
<td>Ion-exchange</td>
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<td>Ravid et al. (44)</td>
<td>574</td>
<td>2–9</td>
<td>By quintiles, risk of progression for cardiovascular end points with GHb in the highest quintile was 14.75</td>
<td>Affinity</td>
</tr>
<tr>
<td>EPIC-Norfolk (47)</td>
<td>4662</td>
<td>2–4</td>
<td>A 1% increase in HbA1c was associated with an ~30% increase in all-cause mortality and a 40% increase in cardiovascular or ischemic heart disease mortality (P &lt;0.001)</td>
<td>Ion-exchange</td>
</tr>
<tr>
<td>Bruno et al. (48)</td>
<td>1967</td>
<td>HbA1c &gt;8.0% was associated with higher concentrations of total cholesterol, triglycerides, and fibrinogen</td>
<td>HPLC (likely ion-exchange)</td>
<td></td>
</tr>
<tr>
<td>Wu et al. (39)</td>
<td>137</td>
<td>5</td>
<td>High HbA1c (10.5% vs 6.9%) was associated with increased cardiovascular morbidity and mortality</td>
<td>Affinity</td>
</tr>
<tr>
<td>Standl et al. (49)</td>
<td>290</td>
<td>10</td>
<td>Higher HbA1c was a significant factor in macrovascular deaths (7.7% in survivors vs 8.2% in deceased)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lehto et al. (50)</td>
<td>1059</td>
<td>7</td>
<td>Risk of stroke was 3- to 5-fold higher in diabetics when HbA1c was &gt;10.7%</td>
<td>Affinity</td>
</tr>
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<td>Klein (38)</td>
<td>2990</td>
<td>10</td>
<td>Hazard ratio for dying was 1.9-fold higher for patients in the 4th quartile of HbA1c compared with the 1st quartile</td>
<td>Ion-exchange</td>
</tr>
<tr>
<td>Kuusisto et al. (51, 52)</td>
<td>229</td>
<td>3.5</td>
<td>HbA1c at baseline was a strong predictor of all cardiovascular events, stroke, and deaths</td>
<td>Ion-exchange</td>
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* In reports where the authors do not clearly specify whether ion-exchange or affinity methods were used, the most likely method has been specified according to the terminology used in reporting GHb results.

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<td>Chowdury and Laker (62)</td>
<td>253</td>
<td>Single point</td>
<td>HbA1c &gt;6.5% was a risk marker for short-term mortality following acute myocardial infarction</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kayaba et al. (63)</td>
<td>2600</td>
<td>Single point</td>
<td>HbA1c concentrations correlated with concentrations of triglycerides, fibrinogen, and factor VII</td>
<td>HPLC (likely ion-exchange)</td>
</tr>
<tr>
<td>Park et al. (64)</td>
<td>1239</td>
<td>8</td>
<td>Highest quintile of GHb &gt;6.7% had a doubling of the relative hazard for ischemic heart disease and fatal cardiovascular disease</td>
<td>Ion-exchange</td>
</tr>
<tr>
<td>EPIC (47)</td>
<td>21000</td>
<td>2–4</td>
<td>In nondiabetic subjects, an increase of 1% in HbA1c was associated with a 28% increase in risk of death (P &lt;0.002) independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking.</td>
<td>Ion-exchange</td>
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reference methods for estimation of HbA$_{1c}$, following a trend for many specific reference methods in clinical chemistry to be based on gas chromatography–mass spectrometry. Roberts et al. (69) and Peterson et al. (70) used ESI-MS to identify those components measured as “HbA$_{1c}$.” In both reports (69, 70), at low GHb concentrations, hemolysates from diabetic patients revealed higher β-chain to α-chain glycation, whereas at high GHb concentrations, multiple β-chain sites were glycated, accompanied by increasing α-chain glycation. In addition, Roberts et al. (69) demonstrated that even at the highest value analyzed for GHb, only a single glucose molecule was added to the multiple glycation sites. They also found reasonably good linear correlations of all established methods compared with ESI-MS, although the latter method generally reported a lower percentage of GHb than the separation methods. Kobold et al. (71) analyzed endoproteinase Glu-C digests of whole-blood samples. Endoproteinase Glu-C cleaves N-terminal segments of the β chains between the two glutamic acid residues at positions 6 and 7, with the resulting fragments containing only a single glycation site at the β-chain N-terminal valine. By this approach, interference by carbamylated and acetylated N-terminal species and by the dimer composed of a glycated α chain and a nonglycated β chain are excluded. In other words, HbA$_{1c}$ as defined by the IFCC is actually measured. However, is it more important to determine glycation on only the β-chain N-terminal valine (which has been defined as HbA$_{1c}$) by the IFCC working group) or to estimate all possible glycation sites in hemoglobin (i.e., the total glycated burden) as with the ESI-MS method without Glu-C digestion of the hemolysates? Overall, measurement of glycation at the N-terminal valine of the β chain is more specific, and a proposed reference system demands an exact knowledge of the analyte to be measured. Alternatively, measurement of all potentially glycated sites might be clinically more relevant, especially at high GHb concentrations. All of these hold promise as candidate reference methods to yield a procedure to address the problem of standardization in GHb testing. However, mass spectrometric methods may not have a primary role in routine laboratory settings in the immediate future because of the expensive and sophisticated hardware and software, the modest throughput, and the technical knowledge required for accurate and reliable results.

Because the development of complications is linked to the accumulation of glycation adducts in tissue proteins, any analytical method that serves as an index of the extent of glycation should clearly be used to guide therapy in diabetes. Although the ion-exchange method does not meet contemporary standards for accuracy, immensely valuable prognostic information has been gathered with this procedure over nearly 2 decades of observing the 1441 and 3867 subjects, respectively, in the DCCT and the UKPDS. Other important studies, both prospective and retrospective, have used either the ion-exchange method or have used methods that correlate to the DCCT method for estimation of GHb. It is clear that near-normal glycemic control is necessary to prevent the development and progression of complications. Moreover, because it is difficult to reverse complications, one cannot justify a clinical trial with another method to confirm the efficacy of glycemic control on diabetic complications, as demonstrated by the DCCT (32) and UKPDS (34). From the results of these clinical trials, it would be unethical to initiate a new prospective trial with treatment groups having different degrees of glycemic control to test the efficacy of the new reference method for GHb. Therefore, regardless of the reference method(s) adopted, the HbA$_{1c}$ concentrations measured in the DCCT and UKPDS will have to be related to values based on the new reference systems because the ESI-MS methods will yield lower values for GHb. Furthermore, this translation must be computationally and efficiently effected because adequate monitoring of glycemic control by GHb estimation is a necessary component of management for the patients and their healthcare providers. The transition to new standards much be completed with caution, i.e., only when the new method’s efficacy can be compared with the ion-exchange method, a procedure used in two major trials and whose values reflect the contemporary clinical standard.

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References


