

## Slow Response to Loss of Glycemic Control in Type 2 Diabetes Mellitus

Jonathan B. Brown, PhD, MPP; Gregory A. Nichols, PhD

**Background:** To achieve glycemic control in type 2 diabetes mellitus, the American Diabetes Association (ADA) recommends intensification of glucose-lowering therapy when the glycosylated hemoglobin (HbA<sub>1c</sub>) level exceeds 8.0%.

**Objective:** To study glycemic control before and after initiation of secondary antihyperglycemic therapy to better understand the pace and patterns of therapeutic failure and clinical responses to failure.

**Study Design:** A retrospective, population-based observational study.

**Patients and Methods:** From a 12-year-old diabetes registry of members of Kaiser Permanente Northwest, a large group-model HMO, we tracked the glycemic control histories of all 570 registrants who, in 1998, added metformin therapy to sulphonylurea monotherapy.

**Results:** The last HbA<sub>1c</sub> level before metformin use averaged 9.4%. Metabolic decompensation accelerated over time. Patients typically spent numerous months at and had several measurements of HbA<sub>1c</sub> >8.0% before a final glycemic spike to >9.0%. Persons experiencing more gradual failure accumulated greater glycemic burdens before changing therapy.

**Conclusions:** The level of HbA<sub>1c</sub> that seemed to trigger glucose-lowering action was 9.0% or higher, not 8.0% as recommended by the ADA. A substantial hyperglycemic peak preceded change in therapy even in this relatively tightly controlled population with type 2 diabetes mellitus. Earlier therapeutic changes, but not more frequent testing, would prevent the glycemic excursions we observed. Low mean HbA<sub>1c</sub> levels in populations do not necessarily indicate that loss of glycemic control is being rapidly addressed for most patients. More research is needed to estimate the impact of these peaks on current well-being and future complications.

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quent urination, but also greatly reduces the risk of microvascular complications<sup>1-3</sup> and may prevent cardiovascular events and death.<sup>4</sup> To guide clinicians and patients in achieving glycemic control, the American Diabetes Association (ADA) recommends measurement of glycosylated hemoglobin (HbA<sub>1c</sub>) levels at least once or twice per year, with intensification of glucose-lowering therapy when levels exceed 8.0% (and a treatment goal of <7.0%).<sup>5</sup> Common therapeutic actions include using an oral antihyperglycemic agent for patients previously managed with diet and exercise alone, substituting or adding a second oral agent when the primary agent loses effectiveness, and initiating insulin therapy, alone or in combination with oral agents.

Simple changes in pharmacotherapy can help persons with HbA<sub>1c</sub> levels >8.0% achieve better control.<sup>6,7</sup> In the present article, we describe mean glycemic control before and after initiation of secondary metformin therapy.

### RESEARCH DESIGN AND METHODS

#### Research Setting and Population

The subjects of this study were members of a not-for-profit, group-model HMO, Kaiser Permanente Northwest (KPNW), in Oregon and southwestern Washington State. Demographically and economically, KPNW members resemble the area population,<sup>8</sup> but members with DM receive more guideline-adherent care and achieve lower-than-average risk factor levels.<sup>9</sup>

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Glycemic control is a major goal of therapy for type 2 diabetes mellitus (DM). Achieving normal or near-normal blood glucose levels not only relieves the symptoms of acute hyperglycemia, such as blurred vision, fatigue, and fre-

From Kaiser Permanente Center for Health Research, Portland, Ore.

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Corresponding author: Jonathan B. Brown, PhD, MPP, Kaiser Permanente Center for Health Research, 3800 N Interstate Ave, Portland, OR 97227-1110. E-mail: jonathan.brown@kpchr.org.

The KPNW registry DM management program has been described in detail elsewhere.<sup>9</sup> Glucose control in the KPNW registry was very good. During the study period, January 1, 1998, to December 31, 1998, HbA<sub>1c</sub> concentration averaged 7.6%. Nearly two thirds of registrants (66.3%) had a mean HbA<sub>1c</sub> level <8%; 87.3% had a mean HbA<sub>1c</sub> level <9%.

During 1998, the clinical recommendation of the Northwest Permanente Medical Group was to initiate pharmacologic treatment of type 2 DM with glyburide and then to add metformin therapy when sulphonylurea (SU) monotherapy no longer controlled hyperglycemia. Therefore, to assess clinical response to loss of glycemic control, we studied the glycemic histories of all 570 registrants who added metformin therapy to SU monotherapy in 1998. For analysis, we divided these individuals into those who added metformin therapy (1) after 1 to 2 years of SU monotherapy, (2) after 2 to 3 years of SU monotherapy, and (3) after ≥3 years of SU monotherapy. We excluded persons who used SU monotherapy for ≤1 year. All analyses were based on the first time that metformin was prescribed.

To ensure complete histories of antihyperglycemic treatment, we included only persons who had their DM diagnosed as members of KPNW (80% of registrants). We assumed that a member was diagnosed by KPNW if he or she had at least 1 full year of membership before diagnosis without any of the following indications of DM: antihyperglycemic drug use, purchase of supplies for blood sugar testing, outpatient diagnostic notations, inpatient discharge diagnoses, participation in DM education, or a diagnostically elevated glucose or HbA<sub>1c</sub> level (using 1997 ADA criteria).<sup>10</sup>

#### Data Sources and Measures

We searched electronic pharmacy records back through 1987 to ascertain drug use history. These records are very complete—95% of KPNW members with DM report getting all or most of their medicines for DM from KPNW pharmacies (data not shown).

All HbA<sub>1c</sub> tests were performed by a single in-house laboratory. During 1998, the laboratory performed 2.3 ambulatory HbA<sub>1c</sub> tests per registrant per year. (Test results obtained during hospital stays, during emergency department visits, and from portable glucometers were not available for analysis.) To determine blood glucose testing rates and levels before the addition of metformin therapy, we searched electronic laboratory records for predefined periods: 0 to 4, 5 to 12, 13 to 24, and 25 to 36 months before the first metformin use. When multi-

ple tests were performed for an individual during a given period, we used the person's first (earliest) result (except during 0-4 months, when we used the result closest to the therapy change). This approach minimized the possibility of bias due to oversampling of patients who were more frequently tested.

To estimate glycemic control after changes in therapy, we sampled the last test performed during months 4 through 12 after the change in therapy, ignoring the first 3 posttreatment months to allow time for physiologic adjustment and dosage titration. All HbA<sub>1c</sub> results were obtained using the Diamat assay (Biorad Laboratories, Hercules, Calif), the standard method used in the Diabetes Control and Complications Trial.<sup>1</sup> The normal range for this assay is 5.05% ± 0.50%.

## RESULTS

Most patients (366 [64.2%] of 570) who added metformin therapy to SU monotherapy in 1998 had been taking SUs for ≥3 years (**Table 1**). Compared with patients who had been using SUs for 25 to 36 months and 13 to 24 months, long-time users were older (63.0 vs 58.4 and 55.6 years;  $P < .001$ ) and had had DM for approximately 4 additional years (6.4 vs 2.8 and 2.2 years;  $P < .001$ ). More than 87% of patients who added metformin therapy to SU monotherapy had had their HbA<sub>1c</sub> level measured by the regional laboratory within 120 days of the change (data not shown), and 80% had tests in each of the 4 previous years; >90% had follow-up testing within 1 year.

In all 3 SU duration groups, HbA<sub>1c</sub> levels >8% had been documented multiple times (**Table 2**). The number of measurements >8% was correlated with duration of SU use, ranging from 2.7 in the shortest use group to 5.2 in those using SUs for ≥37 months. The number of months in SU failure was similarly related to duration of use, ranging from 9.7 to 38.9 months.

The **Figure** graphs mean HbA<sub>1c</sub> levels over time, before and after the addition of metformin therapy to SU monotherapy. Separate lines are shown for persons who added metformin therapy after 13 to 24 months of SU monotherapy, after 25 to 36 months, and after ≥37 months. All 3 subgroups exhibited a common pattern of accelerating (exponential) loss of glycemic control, with almost identical mean HbA<sub>1c</sub> levels during the 4 months immediately before metformin use (9.3%-9.5%;  $P = .78$ ). Mean HbA<sub>1c</sub> levels during the 4 to 12 months after the addition of

**Table 1.** Demographic Characteristics of Patients Adding Metformin Therapy in 1998 After >1 Year of Sulphonylurea (SU) Monotherapy\*

	Duration of SU Use Before Adding Metformin, mo			
	13-24 (n = 113)	25-36 (n = 91)	≥37 (n = 366)	Total (n = 570)
Age in 1998, mean (SEM), y <sup>†</sup>	55.6 (1.03)	58.4 (1.10)	63.0 (0.59)	60.8 (0.48)
Age, y <sup>†</sup>				
<30	0.9	0	0	0.2
30-44	13.3	8.8	3.6	6.3
45-54	39.8	29.7	20.8	26.0
55-64	24.8	30.8	32.0	30.4
65-74	15.9	25.3	24.0	22.6
≥75	5.3	5.5	19.7	14.6
Women	47.8	48.4	49.5	49.0
Duration of DM, mean (SEM), y <sup>†</sup>	2.2 (0.12)	2.8 (0.08)	6.4 (0.13)	5.0 (0.12)
Duration of DM, y <sup>†</sup>				
1-2	72.6	0	0	14.4
>2-3	11.5	86.8	0	16.1
>3	15.9	13.2	100	69.5

\*Data are given as percentages except where indicated otherwise. DM indicates diabetes mellitus.

<sup>†</sup>Differences among SU duration groups were significant at  $P < .05$ .

**Table 2.** Clinical Characteristics of Patients Adding Metformin Therapy in 1998 After >1 Year of Sulphonylurea (SU) Monotherapy

	Duration of SU Use Before Adding Metformin, mo			
	13-24 (n = 113)	25-36 (n = 91)	≥37 (n = 366)	Total (n = 570)
Duration of SU use, y <sup>†</sup>	1.5 (0.03)	2.5 (0.03)	6.2 (0.13)	4.5 (0.12)
Time since first HbA <sub>1c</sub> level >8.0%, mo <sup>†</sup>	9.7 (0.73)	16.7 (1.33)	38.9 (19.23)	30.2 (0.91)
HbA <sub>1c</sub> measurements >8% before metformin addition, no. <sup>†</sup>	2.7 (0.16)	3.5 (0.30)	5.2 (0.18)	4.5 (0.14)

\*Data are given as mean (SEM). HbA<sub>1c</sub> indicates glycosylated hemoglobin.

<sup>†</sup>Differences among SU duration groups were significant at  $P < .05$ .

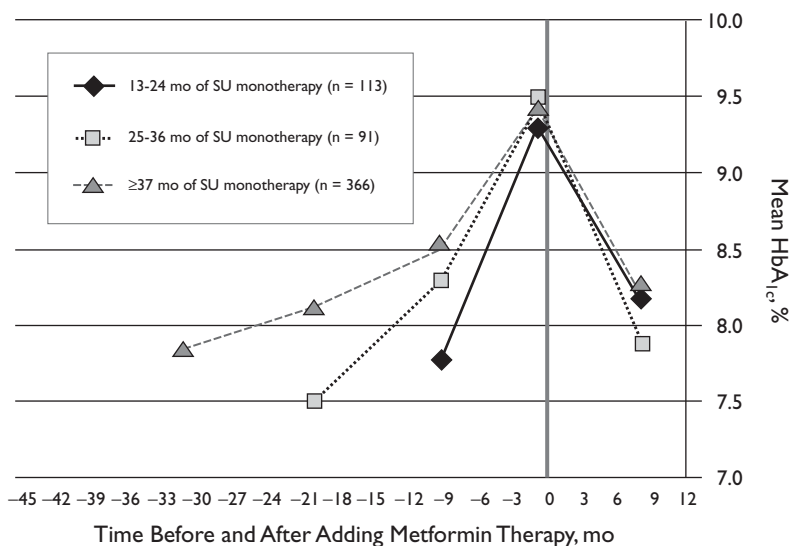
metformin therapy were also similar (7.8%-8.2%;  $P = .19$ ). Thus, some patients lost control quickly and others more slowly, but, on average, all reached HbA<sub>1c</sub> levels substantially >9.0%, and all groups received about the same reduction in HbA<sub>1c</sub> levels once their therapy was changed. However, patients who failed most slowly spent approximate-

ly 2 more years with an HbA<sub>1c</sub> level >8.0% than did patients who failed quickly.

#### CONCLUSIONS

Many patients diagnosed as having DM initiate antihyperglycemic drug therapy immediately. Most

**Figure.** Mean Glycosylated Hemoglobin (HbA<sub>1c</sub>) Levels in Patients Undergoing Sulphonylurea (SU) Monotherapy Before and After Adding Metformin Therapy



of those who wait eventually progress to pharmacotherapy<sup>11,12</sup> and subsequently modify the pharmacotherapy to maintain glycemic control.<sup>11-13</sup> In the KPNW setting, during 1998, nearly all persons with type 2 DM began drug therapy with glyburide, added metformin therapy when SU monotherapy failed,<sup>12,14,15</sup> and then started insulin administration. Despite frequent HbA<sub>1c</sub> measurement (2.3 measurements per year) and a low overall mean HbA<sub>1c</sub> level (7.7%), we found high levels of HbA<sub>1c</sub> before changing antihyperglycemic therapy. Most patients reached a mean HbA<sub>1c</sub> level of approximately 9.4% before new therapy was initiated. The level of HbA<sub>1c</sub> that seems to have triggered action was approximately 9.0%, not 8.0% as recommended by the ADA.<sup>5</sup>

Although population-wide deterioration of mean glycemic control is gradual and generally linear in clinical trial and natural history cohorts,<sup>11,15-17</sup> our results show that for individuals, deterioration can start at any time and accelerates rapidly to a substantial glycemic peak. The health impact of such peaks is not known. In general, chronic elevations of blood sugar increase the risk of microvascular and possibly macrovascular complications of DM.<sup>1-3</sup> Transitional peaks clearly add to the cumulative glycemic burden.<sup>18</sup> In addition, patients might risk extra health problems if subsequent rapid reductions in HbA<sub>1c</sub> levels stimulate the development of accelerated retinopathy, as has been shown

to occur when hyperglycemia is rapidly corrected with insulin and other agents.<sup>19-26</sup> More research is needed to assess the possible deleterious effects of a sawtooth pattern of glycemic control.

If the KPNW clinicians had followed the 8.0% action threshold recommended by the ADA, the peaks that we observed would have been prevented. The reasons that the KPNW clinicians did not act on the 8.0% threshold are unclear, especially in view of their medical group's explicit and—relative to most other clinical goals—strong commitment to do so. Perhaps clinicians began by urging changes in diet and exercise that did not materialize. Clinicians also may have hoped that glycemic increases would be temporary. Because the present study did not capture patients who may have begun to fail

but did not ultimately progress to therapeutic failure, we cannot comment conclusively on the wisdom of such conservative approaches.

Our data indicate that most patients were in mild failure (HbA<sub>1c</sub> >8.0%) for at least several months and had received multiple above-threshold HbA<sub>1c</sub> test results before experiencing more severe hyperglycemia. Thus, more frequent testing cannot be recommended as a remedy for clinicians' lack of response. Once HbA<sub>1c</sub> levels begin accelerating through 9.0%, only a monthly frequency of HbA<sub>1c</sub> testing could detect the acceleration (home glucose monitoring could, however). Instead, to avoid the hyperglycemic excursions we observed, clinicians and patients would have had to make therapeutic changes at the earliest sign of diminishing glycemic control. More research is needed to understand why clinicians do not change therapies more rapidly.

With respect to measuring quality of care in medical care systems, these results indicate that the commonly used process measure, frequency of HbA<sub>1c</sub> measurement, has limited meaning because it does not necessarily imply appropriate follow-up of the results of those tests. In addition, even excellent performance on the more sophisticated measure, populationwide HbA<sub>1c</sub>, does not ensure that loss of glycemic control is being rapidly addressed for most patients.

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