Evaluating Once- and Twice-Daily Self-Monitored Blood Glucose Testing Strategies for Stable Insulin-Treated Patients With Type 2 Diabetes

The Diabetes Outcomes in Veterans Study

RICHARD M. HOFFMAN, MD[1]
JAYENDRA H. SHAH, MD[2,3]
CHRISTOPHER S. WENDEL, MS[2]
WILLIAM C. DUCKWORTH, MD[4]
KAREN D. ADAM, RN[1]
SYED U. BOKHARI, MD[4]
CHERI DALTON, BSN[2]
GLEN H. MURATA, MD[1]

OBJECTIVE — To evaluate once- and twice-daily self-monitored blood glucose testing strategies in assessing glycemic control and detecting hypoglycemia or hyperglycemia in patients with stable insulin-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS — Subjects with stable insulin-treated type 2 diabetes monitored blood glucose four times daily (prebreakfast, prelunch, predinner, and bedtime) for 8 weeks. We correlated mean blood glucose values with HbA_{1c} measured after 8 weeks and determined the number of hypoglycemic (≤3.33 mmol/l) and hyperglycemic (≥22.20 mmol/l) readings captured at the various testing times.

RESULTS — A total of 150 subjects completed the monitoring period; their average age was 67 years, 90% were men, and the mean HbA_{1c} at baseline was 8.0 ± 1.8%. The overall correlation of glucose testing and HbA_{1c} was 0.79 ($P < 0.0001$). Mean blood glucose values for each of the four once-daily testing strategies were significantly correlated with HbA_{1c} ($r = 0.65–0.70$, $P < 0.0001$), as were mean blood glucose values for each of the six twice-daily testing strategies ($r = 0.73–0.75$, $P < 0.0001$). The prebreakfast/prelunch measurements captured the largest proportion (63.6%) of the hypoglycemic readings, the predinner/bedtime measurements captured the largest proportion (66.2%) of hyperglycemic readings, and the prelunch/predinner measurements captured the largest proportion (57.7%) of all out-of-range readings.

CONCLUSIONS — Twice-daily testing strategies, particularly prelunch/predinner, effectively assess glycemic control and capture a substantial proportion of out-of-range readings. However, personal testing strategies will vary depending on an individual's risk for hypoglycemia and hyperglycemia.

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The American Diabetes Association (ADA) recommends that self-monitoring of blood glucose (SMBG) be done on a regular basis for insulin-treated patients with type 2 diabetes (1). Testing should be frequent enough to facilitate the goals of achieving appropriate glycemic control and to detect asymptomatic hypoglycemia (1). More frequent monitoring may be appropriate for poorly controlled patients and for patients who adjust their preprandial short-acting insulin. Stable patients who do not adjust insulin doses require less intensive testing. However, the optimal SMBG testing strategy for these patients is unknown.

Data from the third National Health and Nutrition Examination Survey (NHANES III), collected between 1991 and 1994, provided information on the testing practices of insulin-treated patients (2). Only 39.1% of those performing SMBG tested their sugars daily. Fewer than 10% reported testing two or more times per day, and poorly controlled patients did not test more frequently than well-controlled patients. These results suggest that insulin-treated patients with type 2 diabetes may not be performing SMBG often enough to achieve optimal glycemic control or to avoid hypoglycemia, and certainly not often enough to make frequent insulin adjustments.

The ADA has recommended that efforts be made to substantially increase the appropriate use of SMBG (1). The uncertainties about the frequency and timing of SMBG in type 2 diabetes and the relatively poor compliance with frequent monitoring suggest that strategies are needed to enhance compliance. Additionally, testing strategies must obtain sufficient data to accurately assess glycemic control and patterns of hypoglycemia and hyperglycemia. The purpose of this study is to evaluate once- and twice-daily SMBG testing strategies compared with four-times daily testing in assessing glycemic control and detecting hypoglycemia or hyperglycemia in patients with stable insulin-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Subjects were part of the prospective, multicenter, 1-year observational Diabetes Outcomes in Veterans Study. The study evaluated the role of psychosocial, clinical, and demographic

From the [1]Department of Medicine, New Mexico VA Health Care System, Albuquerque, New Mexico; the [2]Southern Arizona VA Health Care System, Tucson, Arizona; the [3]Departments of Medicine and Radiology, University of Arizona College of Medicine, Tucson, Arizona; and the [4]Department of Medicine, Carl T. Hayden VA Medical Center, Phoenix, Arizona.

Address correspondence and reprint requests to Richard M. Hoffman, MD, New Mexico VA Health Care System, 1501 San Pedro Dr. SE (111GIM), Albuquerque, NM 87108. E-mail: rhoffman@unm.edu.

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Abbreviations: NHANES III, third National Health and Nutrition Examination Survey; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

variables in predicting glycemic control, as measured with HbA_{1c}. The study population was comprised of veterans receiving care at the New Mexico VA Health Care System in Albuquerque, NM; the Carl T. Hayden VA Medical Center in Phoenix, AZ; and the Southern Arizona VA Health Care System in Tucson, AZ. Inclusion criteria for the study were type 2 diabetes diagnosed after age 35 years, therapy with long-acting insulin, and mental competence. We further required stable glycemic control, defined as either not having received new oral agents or not having adjusted insulin doses by >10% or >15 units in the preceding 2 months. Subjects were excluded if they were not enrolled in primary care, had a history of diabetic ketoacidosis, were titrating insulin doses, were unable to test blood glucose regularly, were unlikely to survive 1 year, or abused alcohol or other substances. Other exclusion criteria included chronic liver or pancreatic disease, chronic infectious diseases, endocrinopathies other than diabetes that affected glucose homeostasis, immunocompromised states, and treatment with glucocorticoids or an insulin pump.

We randomly selected potentially eligible subjects from electronic pharmacy profiles reporting prescriptions for at least one daily injection of long-acting insulin. We reviewed medical records to determine eligibility and contacted the primary care provider of each eligible subject for approval to enter the subject into the study. All study participants provided informed consent. The institutional review boards at each medical center approved the study protocol.

At the baseline visit, we obtained data from study subjects on demographics, socioeconomic status, mental status, psychological profiles, diabetes complications and treatments, hypoglycemic medications, comorbidity, and barriers to care. Patients were observed obtaining an SMBG reading and given further training if necessary. We measured HbA_{1c} and instructed subjects to test their blood glucose prebreakfast, prelunch, predinner, and at bedtime everyday for 8 weeks. Whole-blood readings were obtained with Comfort Curve test strips and an AccuChek Complete electronic blood glucose meter (Roche Diagnostics, Indianapolis, IN). The meter, which is calibrated to give plasma-like values, can store 1,000 readings. The SD for low readings with this monitoring system is 0.15 mmol/l (3). Subjects returned at 4 and 8 weeks to download meters and measure HbA_{1c}. HbA_{1c} was measured at each study site with a Tosoh high-performance liquid chromatography method. The normal range for HbA_{1c} with this assay is 4–6%, and the coefficient of variation is 4.7% for low controls (HbA_{1c} 5%) and 2.8% for high controls (HbA_{1c} 10.2%). We encouraged patients to comply with the testing protocol but provided no treatment recommendations.

Statistical analysis

Blood glucose meter data were downloaded and entered into an Access database. We used descriptive statistics to assess patient characteristics, including age, race/ethnicity, diabetes duration, treatment, control, and compliance with testing. Because we were interested in four-times daily testing results, we excluded subjects who missed either 4 or more consecutive days of monitoring or who obtained four daily readings fewer than 7 days during the study period.

We determined mean blood glucose values and SDs for each individual testing time, for each combination of twice-daily testing, and for all four testing times combined. We also evaluated once-daily testing strategies by rotating the analyzed testing time result each successive day, beginning with prebreakfast on the first day and ending with bedtime on the fourth day. Similarly, we evaluated rotating testing times for twice-daily testing strategies by analyzing results obtained from alternating days of *1*) prebreakfast/predinner readings with prelunch/bedtime readings, *2*) prebreakfast/prelunch with predinner/bedtime, and *3*) prebreakfast/bedtime with prelunch/predinner. Bivariate linear regression was performed to determine the correlation of mean blood glucose readings for various times of day with the 8-week HbA_{1c}.

We also described the occurrence of hypoglycemic readings (defined as blood glucose ≤3.33 mmol/l) and hyperglycemic readings (defined as blood glucose ≥22.20 mmol/l). We used the McNemar test to compare the yield of out-of-range readings captured by the various twice-daily testing strategies. Statistical tests were performed with the Statistica software package (4).

Table 1—*Subject characteristics*

Characteristics	
n	150
Age (years)	65.6 ± 9.6
Sex (male)	95%
Ethnicity/race	
Non-Hispanic white	73%
Hispanic	15%
African-American	10%
Other	2%
Duration of diabetes (years)	14.6 ± 9.5
Long-acting insulin†	
NPH	67%
Ultralente	3%
70/30 Insulin	30%
Lente	2%
Duration of insulin treatment (years)	8.1 ± 8.2
Mean daily insulin dose (units)	66.6 ± 49.4
Mean daily number of insulin doses	2.1 ± 0.6
Oral agents	33%
Baseline HbA_{1c} (%)	8.0 ± 1.8

Data are means ± SD, unless otherwise indicated. †Total exceeds 100% because some patients were using NPH in the evening and 70/30 insulin in the morning.

RESULTS — We enrolled 247 subjects into the blood glucose meter study, and 212 subjects completed the 8-week monitoring period. We excluded 48 subjects for noncompliance and an additional 14 subjects whose follow-up HbA_{1c} was not obtained by 4 days after the end of monitoring. Table 1 shows the baseline characteristics of the 150 study subjects who completed the monitoring protocol. Subjects were elderly men with longstanding diabetes and high daily insulin requirements.

Study participants obtained, on average, 187 of the 224 required glucose readings (84.2%) during the 8-week testing protocol, representing 28,956 prospectively collected measurements. The overall mean ± SD for all glucose readings was 9.55 ± 2.2 mmol/l and for HbA_{1c} measured at 8 weeks was 7.48 ± 1.43%. The correlation coefficient between the mean glucose from all four testing times combined and the 8-week HbA_{1c} was 0.79 ($P < 0.0001$). The correlation coefficients between mean glucose and HbA_{1c} for the once-daily testing strategies are shown in Table 2. The correlation coefficients ranged from 0.65 to 0.70, explaining 42–49% of the variance in HbA_{1c}, and were all highly significant. The correlation co-

Table 2—*Correlation of mean glucose by testing time(s) of day with 8-week HbA_{1c}*

Testing time	Glucose (mmol/l)	Correlation coefficient	*P*
Prebreakfast	8.50 ± 2.39	0.67	<0.0001
Prelunch	9.42 ± 2.54	0.67	<0.0001
Predinner	9.70 ± 2.68	0.70	<0.0001
Bedtime	10.75 ± 2.51	0.65	<0.0001
Prebreakfast/prelunch	8.93 ± 2.26	0.73	<0.0001
Prebreakfast/predinner	9.08 ± 2.31	0.75	<0.0001
Prebreakfast/bedtime	9.53 ± 2.12	0.75	<0.0001
Prelunch/predinner	9.56 ± 2.45	0.74	<0.0001
Prelunch/bedtime	10.09 ± 2.24	0.74	<0.0001
Predinner/bedtime	10.21 ± 2.40	0.74	<0.0001

Data are means ± SD.

efficients between mean glucose and HbA_{1c} for the twice-daily testing strategies are also shown in Table 2. The correlation coefficients ranged from 0.73 to 0.75, explaining 53–56% of the variance in HbA_{1c}, and were all highly significant.

We found that 2% of all glucose readings were ≤3.33 mmol/l, and 64% of the subjects recording at least one hypoglycemic reading. Nearly 1% of all glucose readings were ≥22.20 mmol/l, and 38% of the subjects recorded at least one hyperglycemic reading. The proportions of out-of-range readings—hypoglycemic, hyperglycemic, and combined—captured by each of the single and twice-daily testing strategies are shown in Table 3. The prebreakfast/prelunch measurements captured the largest proportion of the hypoglycemic readings, although the yield from prelunch/predinner testing was statistically equivalent. The predinner/bedtime measurements captured the largest proportion of hyperglycemic readings and produced a statistically higher yield than any other testing strategy. Finally, the prelunch/predinner measurements captured the largest proportion of all out-of-range readings, although the yields from prebreakfast/prelunch and prelunch/bedtime testing were statistically equivalent.

We evaluated the possible benefit of varying the time of the measurements in the once- and twice-daily testing strategies. Rotating the once-daily testing strategies increased the correlation with HbA_{1c} to 0.75, explaining 56% of the variance in HbA_{1c}, and captured 26.4% of hypoglycemic readings, 20.1% of hyperglycemic readings, and 24.2% of all out-of-range readings. When we rotated the twice-daily testing strategies, the overall correlations with HbA_{1c} also increased, ranging from 0.77 to 0.79, and 59–62% of the variance in HbA_{1c} could be explained. The rotating strategy of prebreakfast/predinner alternating with prelunch/bedtime captured 51.9% of hypoglycemic readings, 50.6% of hyperglycemic readings, and 51.4% of all out-of-range readings. However, the fixed strategy of daily prelunch/predinner testing captured a significantly greater proportion of hypoglycemic readings (60.2%, $P < 0.009$) and total out-of-range readings (57.7%, $P < 0.02$), although the proportion of hyperglycemic readings was similar (52.8%, $P = 0.66$). Rotating the other twice-daily strategies, prebreakfast/prelunch with predinner/bedtime and prebreakfast/bedtime with prelunch/predinner, also slightly increased the correlation with HbA_{1c}. However, these strategies captured significantly fewer hypoglycemic readings and out-of-range readings than daily prelunch/predinner testing.

CONCLUSIONS — We evaluated 8 weeks of prospectively collected blood glucose meter readings from a population of stable insulin-treated patients with type 2 diabetes, comprised mostly of older men with fair glycemic control. Overall mean blood glucose results from the four daily conventional testing times, prebreakfast, prelunch, predinner, and prebedtime, were each significantly correlated with HbA_{1c} measured at the end of the 8-week monitoring period. The correlation coefficients between HbA_{1c} and the means of the four once-daily testing strategies ranged from 0.65 to 0.70 (all statistically significant). The correlation coefficients further increased (range 0.73–0.75) with the twice-daily testing strategies (all statistically significant). Rotating once- and twice-daily testing strategies produced marginally higher correlation coefficients (range 0.77–0.79).

We found that out-of-range readings were commonly recorded. The highest proportion of hypoglycemic readings occurred prelunch, and the highest proportion of hyperglycemic readings occurred at bedtime. Each of the twice-daily testing strategies captured different proportions of these out-of-range readings. The combinations of testing prebreakfast/prelunch and prelunch/predinner

Table 3—*Proportion of out-of-range readings captured by testing time(s)*

Testing time	Hypoglycemic readings (%)	Hyperglycemic readings (%)	Out-of-range readings (%)
Readings (*n*)	530	269	799
Prebreakfast	24.7	12.6	20.7
Prelunch	38.9	21.2	32.9
Predinner	21.3	31.6	24.8
Bedtime	15.1	34.6	21.7
Prebreakfast/prelunch	63.6*	33.8	53.6†
Prebreakfast/predinner	46.0	44.2	45.2
Prebreakfast/bedtime	39.8	47.2	42.3
Prelunch/predinner	60.2*	52.8	57.7†
Prelunch/bedtime	54.0	55.8	54.6†
Predinner/bedtime	36.4	66.2‡	46.4

*Results from these testing times are statistically equivalent and have a significantly higher yield of hypoglycemic readings (≤3.33 mmol/l) than all other testing strategies. †Results from these testing times are statistically equivalent and have a significantly higher yield of out-of-range readings than all other testing strategies. ‡Results from this testing time have a significantly higher yield of hyperglycemic readings (≥22.20 mmol/l) than all other testing strategies.

captured the highest yield of hypoglycemic readings. Testing predinner/prebedtime captured the highest yield of hyperglycemic readings. The highest yield of out-of-range readings came from the combination of testing prelunch/predinner, followed by prelunch/bedtime and prelunch/prebreakfast. Overall, the prelunch/predinner testing strategy was the most effective because it captured the highest yield of out-of-range readings and hypoglycemic readings and the second highest yield of hyperglycemic readings. Compared with prelunch/predinner testing, the rotating strategies for twice-daily testing captured significantly fewer hypoglycemic and out-of-range readings.

Our results have implications for glucose-monitoring strategies. Although the ADA recommends blood glucose meter testing frequently enough to assess glycemic control and reduce the risk of hypoglycemic events, testing compliance is often poor. The majority of subjects in the NHANES III were testing less than once daily (2). When testing infrequently, patients often obtain only morning fasting readings. Although these values can be highly correlated with glycemic control (5–8), we found that correlations with HbA_{1c} were equally high for the prelunch, predinner, and bedtime readings.

Avignon et al. (9) also reported that fasting plasma glucose levels were not necessarily the best predictors of glycemic control. These investigators measured HbA_{1c} and four readings of plasma glucose (prebreakfast, prelunch, postlunch, and extended postlunch) during a single day in 66 non–insulin-treated outpatients with type 2 diabetes. The postlunch readings were most correlated with HbA_{1c} ($r = 0.81$, $P = 0.009$), followed by the extended postlunch readings ($r = 0.78$, $P = 0.032$). The prebreakfast readings were not significantly correlated ($r = 0.62$, $P = 0.079$), and the authors concluded that the postlunch readings should be used to supplement or replace the fasting readings. Other investigators have reported similar findings (10,11). However, all of these studies were limited because subjects were studied for only 1 day and in a controlled laboratory setting. Our results are more generalizable to clinical care because we were able to demonstrate associations between glycemic control and multiple glucose measurements obtained over a much longer study period in subjects who were not in a controlled research setting.

Choosing an effective glucose-monitoring strategy also depends on capturing out-of-range readings. We found no literature looking at the yield of combining multiple testing times to detect hypoglycemic or hyperglycemic readings. Our findings suggest that twice-daily testing strategies can capture a substantial proportion of out-of-range readings, particularly the prelunch/predinner readings, and present a reasonable alternative to four-times daily testing. Rotating strategies captured fewer out-of-range readings than the prelunch/predinner testing strategy. With twice-daily testing, there is no optimal strategy for capturing both hypoglycemic and hyperglycemic readings. Therefore, testing strategies will be based on the individual's risk for hypoglycemia or hyperglycemia.

There were some limitations to our study. Subjects were predominantly older male veterans with type 2 diabetes, and all were using long-acting insulin. Results may not be applicable in other populations, especially for patients treated with diet alone or oral hypoglycemic agents. We did not obtain delayed postprandial readings throughout the day, although the bedtime readings were usually obtained ~3 h after the evening meal. The postmeal glucose excursions captured by postprandial readings are hypothesized to better explain glycemic control, and results from these testing times may be better correlated with HbA_{1c} (12). We also did not evaluate whether subjects with hypoglycemic readings were symptomatic. Our study design, however, was consistent with the ADA objective of using SMBG to detect asymptomatic hypoglycemia (1). Medications can be adjusted based on the timing and frequency of these hypoglycemic readings, potentially preventing symptomatic episodes. Hypoglycemic readings were often recorded in our study; without data on symptoms, we may have overestimated their occurrence. However, the AccuChek Complete monitoring system is very precise (3), and the mean hypoglycemic reading in our study was 2.18 ± 0.48 mmol/l (means ± SD). This suggests that the great majority of hypoglycemic readings (≤3.33 mmol/l) were accurate.

We found that readings obtained from once- and twice-daily testing strategies were almost as highly correlated with HbA_{1c} as readings obtained from four-times daily testing. For patients performing once-daily testing, a rotating strategy (alternating testing times on successive days) could explain more of the variance in HbA_{1c} than any of the fixed once-daily testing strategies. The rotating once-daily testing strategy also captured nearly a quarter of the out-of-range readings, suggesting that patients testing once daily should obtain readings from different times of day. The twice-daily testing strategies explained a significant amount of the variance in HbA_{1c} and captured a substantial proportion of hypoglycemic and hyperglycemic readings. Measuring prelunch/predinner readings appeared to be the best overall twice-daily testing strategy because the correlation with HbA_{1c} was high ($r = 0.74$) and these measurements captured the statistically highest yield of hypoglycemic and combined out-of-range readings. By rotating the timing of the twice-daily strategies, we explained more of the variance in HbA_{1c} than any of the fixed twice-daily strategies, but the yield in capturing out-of-range readings decreased by ~10%. However, the rotating strategies, particularly alternating prelunch/predinner with prebreakfast/bedtime readings, are intuitively appealing because medication adjustments can target glucose readings at different times of day.

Our findings are relevant to clinical practice because the NHANES III reported that ~60% of insulin-treated patients with type 2 diabetes tested at least once weekly, including 39.1% who tested everyday (2). Although we do not know whether these testing patterns are appropriate for individual patients, our strategies are reasonable for optimizing the yield of testing for the many patients who are testing at these frequencies. Personal testing strategies, however, will vary depending on an individual's risks for hypoglycemia and hyperglycemia. Further prospective studies are needed to evaluate the efficacy, safety, and compliance of these testing strategies.

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