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A Single-Center, Open, Comparative Study of the Effect of Using Self-Monitoring of Blood Glucose to Guide Therapy on Preclinical Atherosclerotic Markers in Type 2 Diabetic Subjects

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Abstract

Background:

The aim of our study was to determine the effect of treatment based on preprandial and postprandial self-monitoring of blood glucose (SMBG) on the progression of carotid intima-medial thickness (CIMT) in noninsulin-treated type 2 diabetes mellitus (T2DM) subjects.

Methods:

In this 18-month prospective trial, we recruited subjects 18–70 years of age, treated with metformin and sulfonylurea, with a standardized hemoglobin A1c (HbA1c) level ≤9.0%. Subjects were randomized to use of fasting/preprandial (FP) SMBG results to adjust evening medication or use of postprandial (PP) SMBG results to adjust morning medication. The primary end point was change in CIMT; change in HbA1c was a secondary end point.

Results:

Of the 300 subjects randomized, 280 (140 in each group) completed all biochemical tests and CIMT analysis. Carotid intima-medial thickness was reduced significantly in PP subjects from 0.78 (±0.15) mm to 0.73 (±0.14) mm ($p < 0.005$), but no significant CIMT reduction was seen in FP subjects. A significant reduction in HbA1c was also seen in the PP group ($p < 0.005$) but not in the FP group 1 ($p = 0.165$). Significant improvements in body mass index ($p = 0.038$), waist circumference ($p < 0.001$), systolic blood pressure ($p = 0.008$), and serum cholesterol ($p = 0.02$) were also seen in PP subjects but not in FP subjects.

Conclusion:

Use of postprandial SMBG data to adjust therapy was associated with a significant regression of carotid intima-medial thickening and a reduction in HbA1c in T2DM, whereas no significant improvement in these parameters was seen in subjects who used fasting/preprandial SMBG data for therapy adjustment.

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Abbreviations: (BG) blood glucose, (BMI) body mass index, (CAD) coronary artery disease, (CIMT) carotid intima-medial thickness, (ECG) electrocardiogram, (FP) fasting/preprandial, (HbA1c) hemoglobin A1c, (HPLC) high-performance liquid chromatography, (PP) postprandial, (SECURE) Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E, (SMBG) self-monitoring of blood glucose, (T2DM) type 2 diabetes mellitus

Keywords: carotid intima-medial thickness, diabetes, postprandial, preprandial, self-monitoring

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Introduction

Coronary artery disease (CAD) is the most common and life-threatening complication associated with type 2 diabetes mellitus (T2DM). The risk for CAD among people with diabetes is two- to fourfold greater than in nondiabetic individuals.[1,2]

Coronary artery disease is one of the clinical end points of atherosclerosis, which in its earlier stages involves both functional and structural changes in the arteries. Structural changes can be assessed by studying the carotid intima-medial thickness (CIMT).[3] This preclinical atherosclerotic marker has gained wide recognition in the field of cardiology, as it is a useful surrogate marker for CAD and can also be used in studies on the prevention of CAD.[4,5]

Epidemiological analyses have shown a strong association between postprandial and postchallenge glycemia and cardiovascular risk and outcomes.[6–8] In a randomized trial[9] that assessed the effect of repaglinide and glyburide on CIMT, a reduction of postprandial hyperglycemia was associated with CIMT regression irrespective of the decrease in hemoglobin A1c (HbA1c) levels.

Although there has been a growing focus on the effects of postprandial hyperglycemia on cardiovascular risk, we have found no prospective studies that specifically looked at the effect of preprandial hyperglycemic control on atherosclerosis. Hence there is a need for identifying whether control of preprandial hyperglycemia or postprandial hyperglycemia is more effective in retarding the progression of atherosclerosis. Understanding the relationship between glucose levels and atherosclerotic risk and outcomes would be beneficial in planning treatment policies for both T2DM patients and people who are at risk for developing diabetes and coronary artery disease.[10,11]

To address this need, we conducted a study to determine the relationship of progression of CIMT with treatment based on preprandial and postprandial self-monitoring of blood glucose (SMBG) and laboratory measurements in T2DM subjects. Our hypothesis was that targeting a postprandial treatment goal of <140 mg/dl compared to a preprandial treatment goal of <110 mg/dl (as measured by SMBG) is more effective in preventing the progression of CIMT.

Methods

Subjects

This prospective, randomized, 18-month trial recruited 359 noninsulin-treated T2DM subjects from the Madras Diabetes Research Foundation, Chennai, India. The trial was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.[12] All subjects provided written informed consent. Eligible subjects had the following characteristics: age 18 to 70 years; HbA1c ≤9.0%; body mass index (BMI) ≤30 kg/m^2; willing to perform SMBG several times throughout the study duration; and treated with a sulfonylurea and metformin. Subjects treated with insulin, thiazolidindiones, glitinides, or α-glucosidase inhibitors were excluded. Also excluded were subjects with advanced diabetic complications, angina pectoris, transient ischemic attacks, abnormal electrocardiogram (ECG), cerebrovascular accident within 6 months prior or elevated blood pressure (systolic >140 mm Hg, diastolic >95 mm Hg); subjects with controlled hypertension were not excluded. Baseline characteristics of the study population are presented in **Table 1**.

Protocol

At screening (visit 1), 359 subjects underwent a complete medical examination and assessment of laboratory values and other measures to determine eligibility for study enrollment. At 2 weeks (visit 2), baseline values for CIMT and adverse events were collected for 300 subjects who were randomized to use of fasting/preprandial (FP) SMBG data to adjust therapy or use of 2-hour postprandial (PP) SMBG data to adjust therapy.

The FP subjects (n = 143) were to perform fasting/preprandial SMBG three times per week (at different meals) with a fasting/preprandial glucose target of <110 mg/dl.[13,14] The average of three readings was used. The evening dose of sulfonylurea/metformin was to be increased to the maximum dose if fasting/preprandial glucose values were above >110 mg/dl. The PP subjects (n = 157) were to perform 2-hour postprandial SMBG three times per week following the largest meal of the day selected with a postprandial glucose target of <140 mg/dl.[13,14] The morning dose of sulfonylurea/metformin was to be increased to the maximum dose if 2-hour postprandial glucose values were >140 mg/dl. If the postprandial target was still not met on the

α-glucosidase inhibitor, acarbose was added. If the fasting target was not met, pioglitazone was added along with the evening meal and antidiabetic medication. All dosage changes were made by the health care provider (physician) at clinic visits. Subjects were seen again at 2 weeks (visit 3) and 1 month (visit 4) and then every 3 months for the next 18 months (visits 5–10).

Subjects in both groups were supplied with a diary and a blood glucose (BG) meter (One Touch Basic Plus, LifeScan, Inc., Milpitas, CA) and received instructions for calibration and operation of the meter. Subjects were advised to avoid sugar and sweet foods and to follow a standardized diabetic diet consisting of moderate carbohydrate (55–60%) and protein (20–25%) and low fat (10–15%). Subjects received no specific dietary instructions for addressing elevated fasting/preprandial or postprandial glucose levels.

Table 1.
Baseline Characteristics of Study Population

Variable	FP arm (fasting/preprandial SMBG) (n = 143)	PP arm (postprandial SMBG) (n = 157)	p value
Age (years)	51 ± 9	52 ± 8	0.414
Gender (male)	85 (59%)	96 (61%)	0.764
Body mass index (kg/m^2)	25.7 ± 2.7	25.1 ± 2.8	0.060
Mean diabetes duration (years)	4.6 (± 4.5)	4.0 (± 3.6)	0.230
Waist (cm)	90.7 ± 7.7	90.5 ± 8.0	0.867
Systolic blood pressure (mm Hg)	123 ± 15	126 ± 15	0.116
Diastolic blood pressure (mm Hg)	77 ± 10	76 ± 10	0.731
Fasting blood glucose (mg/dl)	128 ± 30	123 ± 31	0.560
Postprandial blood glucose (mg/dl)	198 ± 59	207 ± 62	0.178
HbA1c (%)	7.3 ± 0.83	7.2 ± 0.87	0.648
Serum cholesterol (mg/dl)	168 ± 33	175 ± 32	0.064
Serum triglycerides (mg/dl)	138 ± 68	155 ± 81	0.061
High-density lipoprotein cholesterol (mg/dl)	41 ± 9	43 ± 13.0	0.318
Low-density lipoprotein cholesterol (mg/dl)	98 ± 32	101 ± 31	0.431
Very low-density lipoprotein cholesterol (mg/dl)	27 ± 14	29 ± 14	0.262
C-reactive protein (mg/dl)	2.94 ± 2.72	2.97 ± 2.82	0.925
Intima-medial thickness (right common carotid, mm)	0.74 ± 0.22	0.78 ± 0.15	0.279

Adherence

Overall adherence was monitored continually by contacting subjects via telephone at least once or twice per month to inquire about BG levels. Home visits were also made to assess subject compliance. Subjects who showed less interest toward the study were encouraged by more frequent telephone calls and home visits. Adherence to the recommended dietary modification was tracked at every visit by regular diet review according to a standardized format. Adherence to the algorithm was tracked through performance of BG testing at the center, as well as a review of downloaded SMBG data and patient diaries at all study visits.

Laboratory and Other Measurements

Blood samples were collected and processed after the subject had fasted for 8 hours. Hemoglobin A1c levels were obtained at baseline, month 6, month 12, and month 18 using high-performance liquid chromatography (HPLC) technology (Variant II Instruments; Bio-Rad Laboratories, Hercules, CA), which have HbA1c calibration traceable to the International Federation for Clinical Chemistry standard, and HPLC results were aligned to the Diabetes Control and Complications Trial. Measurement of fasting plasma glucose was performed at all visits; lipid panel and measurements of thyroid function, C-reactive protein, liver function, urea, and creatinine were performed at baseline, month 6 (visit 6), month 12 (visit 8), and month 18 (visit 10). Subjects received a 12-lead ECG evaluation at screening and month 18 (visit 10) or early termination visit.

Measurement of Carotid Intima-Medial Thickness

The intima-medial thickness of carotid arteries was determined using a high-resolution, B-mode ultrasonography system (Logic 400; General Electric, Milwaukee, WI), having an electric linear transducer midfrequency of 7.5 MHz. Images obtained were recorded and photographed. Scanning was done for an average of 20 minutes. The CIMT was measured as the distance from the leading edge of the first echogenic line to the second echogenic line.[3] Six well-defined arterial wall segments were measured in the right carotid system: the near wall and far wall of the proximal 10 mm of the internal carotid artery, the carotid bifurcation beginning at the

tip of the flow divider and extending 10 mm below this point, and the arterial segment extending 10 mm below the bifurcation in the common carotid artery. Essential in defining these segments is identification of a reliable longitudinal marker, which is the carotid flow divider as performed in the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE).[15] This method was standardized at our center, and, to check quality, the video tapes were sent to Hamilton, Canada, which was the central laboratory for SECURE. Both the patients and the radiologist were blinded to the CIMT results.

With respect to the accuracy of measurements obtained by B-mode imaging as compared with pathologic findings, an early study by Pignoli and colleagues[3] demonstrated an error of less than 20% for measurements in 77% of normal and pathologic aortic walls. They also found no significant difference between B-mode-determined intima-medial thickness in the common carotid arteries evaluated *in vitro* and that determined by this method *in vivo* in young subjects, indicating that B-mode imaging is a useful tool for detecting and monitoring changes in intima-medial thickness, allowing the evaluation of changes in the arterial wall in areas without localized plaques.

Safety Assessments

Safety assessments measured adverse events, including severe hypoglycemic events, severe hyperglycemic events, and other serious adverse events. A severe hypoglycemic event was defined as a clinical episode of hypoglycemia, resulting in seizure or coma, requiring hospitalization, intravenous glucose or glucagon, or any hypoglycemia that required assistance from another person. These episodes were reported by subjects in their workbooks. Incidence and frequency of serious adverse events were documented and assessed.

Statistical Analysis

Key response variables, CIMT and arterial stiffness, were compared to initial baseline values for the two groups separately. Changes in CIMT and arterial stiffness between baseline and final visit were compared by paired t test. Paired differences based on longitudinal data of month 12 versus baseline and month 18 versus baseline were compared for the two treatment groups. Student's t test or analysis of variance was used for comparing mean values of the biochemical parameters. Frequency of hypoglycemia in the two groups was computed for each patient to assess hypoglycemia risk and the association with CIMT and HbA1c regression. A p value <0.05 was considered significant. All statistical analyses were performed by Software SAS® version 9.2 (SAS Institute, Cary, SC).

Results

A total of 300 subjects between the ages of 18 and 70 were enrolled in the study. At randomization, 143 subjects were assigned to the FP group and 157 were assigned to the PP group; 8 subjects withdrew from the study. A total of 280 subjects completed the CIMT study, 140 in each group. Analyses of this data set are presented in this report. Demographic variables of age, HbA1c, and other characteristics were similar at baseline for subjects in both study groups (**Table 1**).

At the study end, the number of subjects who were on maximum medication dosages increased from 31 at baseline to 45 at 18 months in FP subjects and 39 to 69 in PP subjects (**Table 2**). The increase from baseline in the number of PP subjects at maximum metformin dosage was significant ($p = 0.026$).

There was no difference between groups regarding the number of patient phone calls made prior to clinic visits (2920 FP calls versus 2914 PP calls) or the number of home visits made to subjects who were unreachable by phone (208 FP home visits versus 204 PP home visits).

Changes in Carotid Intima-Medial Thickness

Subjects in the PP group showed a significant reduction in CIMT ($p < 0.005$), whereas there was no change in CIMT in FP subjects (**Table 3**). Slight but significant reductions in heart rate ($p = 0.032$) were also seen in PP subjects.

Changes in Glycemic Status

A significant reduction in HbA1c was seen in PP subjects ($p < 0.005$) but not in FP subjects ($p = 0.165$)(**Table 4**). Seventy (50%) FP subjects achieved 7% HbA1c by month 18, compared to 82 (54%) PP subjects. Both study groups showed a statistically significant reduction in their targeted BG levels compared to baseline (**Table 4**).

Changes in Other Metabolic Variables

The PP subject group showed significant improvement in several metabolic variables, including BMI ($p = 0.038$), waist circumference ($p < 0.001$), systolic blood pressure ($p < 0.008$), and serum cholesterol ($p < 0.02$); however, there was a slight but statistically significant ($p < 0.010$) reduction in HDL cholesterol (**Table 3**). Apart from a

Table 2.
Change in Number of Subjects at Maximum Dosages of Medication

	FP (fasting/preprandial SMBG) arm			PP (postprandial SMBG) arm		
	Baseline visit (n = 140)	Final visit (n = 140)	p value	Baseline visit (n = 140)	Final visit (n = 140)	p value
Maximum metformin (2000 mg/day)	13	20	0.216	10	23	0.026[a]
Maximum sulfonylurea (15 mg/day)	16	19	0.642	27	35	0.342
Maximum metformin and sulfonylurea	2	6	0.161	2	11	0.003[a]

[a] A p value <0.05 was considered significant.

Table 3.
Comparison of Carotid Intima-Medial Thickness (CIMT) and Heart Rate between Baseline and Final Visit of Preprandial and Postprandial Arms

Variable	FP (fasting/preprandial SMBG) arm			PP (postprandial SMBG) arm		
	Baseline visit (n = 140)	Final visit (n = 140)	p value	Baseline visit (n = 140)	Final visit (n = 140)	p value
CIMT (right common carotid, mm)	0.74 ± 0.22	0.74 ± 0.14	0.730	0.78 ± 0.15	0.73 ± 0.14	0.005[a]
Heart rate	78.1 ± 11.2	77.0 ± 13.1	0.399	78.2 ± 15.5	75.2 ± 14.9	0.032[a]

[a] A p value <0.05 was considered significant.

Table 4.
Comparison between Baseline and Final Visit of Preprandial and Postprandial Arms

Variable	FP (fasting/preprandial SMBG) arm			PP (postprandial SMBG) arm		
	Baseline visit (n = 140)	Final visit (n = 140)	p value	Baseline visit (n = 140)	Final visit (n = 140)	p value
Body mass index (kg/m^2)	25.7 ± 2.7	25.6 ± 2.8	0.460	25.1 ± 2.8	24.9 ± 3.0	0.038[a]
Waist (cm)	90.7 ± 7.7	90.1 ± 7.3	0.235	90.5 ± 8.0	88.2 ± 10.5	0.001[a]
Systolic blood pressure (mm Hg)	123 ± 15	123 ± 16	0.949	126 ± 15	122 ± 17	0.008[a]
Diastolic blood pressure (mm Hg)	77 ± 10	76 ± 9	0.326	76 ± 10	77 ± 11	0.724
Fasting blood glucose (mg/dl)	128 ± 30	120 ± 21	0.003[a]	—	—	—
Postprandial blood glucose (mg/dl)	—	—	—	209 ± 61	180 ± 54	0.002[a]
HbA1c (%)	7.3 ± 0.8	7.1 ± 1.2	0.165	7.2 ± 0.9	6.9 ± 1.13	0.005[a]
Serum cholesterol (mg/dl)	168 ± 33	166 ± 33	0.517	176 ± 31	168 ± 41	0.020[a]
Serum triglycerides (mg/dl)	138 ± 68	148 ± 85	0.082	155 ± 82	151 ± 91	0.569
High-density lipoprotein cholesterol (mg/dl)	41 ± 9	41 ± 13	0.377	43 ± 13	40 ± 11	0.010[a]
Low-density lipoprotein cholesterol (mg/dl)	98 ± 32	98 ± 34	0.184	101 ± 31	99 ± 33	0.511
Very low-density lipoprotein (mg/dl)	27 ± 14	27 ± 11	0.638	29 ± 14	29 ± 17	0.993
C-reactive protein (mg/dl)	2.94 ± 2.75	2.93 ± 2.51	0.833	2.92 ± 2.77	2.98 ± 2.88	0.791

[a] A p value <0.05 was considered significant.

reduction in fasting glucose, FP subjects showed no significant changes from baseline.

Safety and Adverse Events

There were no incidents of severe hypoglycemia; however, mild hypoglycemia was reported in a few patients. Severe adverse events in the FP group included one CAD, one acute pancreatitis, two chest discomfort (same patient), one generalized seizure, and one fall. One myocardial infarction resulting in death occurred in the PP group. None of these incidents were considered to be associated with diabetes treatment.

Discussion

This prospective, randomized, 18-month trial demonstrated that use of postprandial SMBG data to adjust therapy is strongly associated with regression of carotid intima-medial thickness and improvement in overall glycemic control in noninsulin-treated T2DM subjects. Although subjects in both groups showed a statistically significant reduction in their targeted BG levels, the reduction of postprandial glucose in PP subjects (–29 mg/dl) from baseline was more clinically significant compared with the reduction in fasting/preprandial glucose (–8 mg/dl) in FP subjects.

A key limitation of our study was reliance on self-reported data to assess dietary modifications. Although subjects did not receive specific instructions for modifying their eating based on SMBG readings, we do not know whether subjects did, in fact, make significant changes (total calorie or meal composition) in response to their SMBG results. Given that the medications used in the study do not target postprandial glucose primarily, it is plausible that subjects, particularly those in the PP group, may have been more aggressive in modifying their eating in order to better manage their BG levels. It has been shown that keeping a diary and recording eating habits along with SMBG readings encourage subjects to reflect more on their disease and the measures to improve their present status.[16] Dietary modifications may also explain reductions in BMI, waist circumference, and possibly heart rate due to weight loss. However, the cause of the small but statistically significant reduction in high-density lipoprotein cholesterol levels in the PP group (which is at odds with regression in CIMT) remains unknown and may simply be an anomaly.

Another limitation of the study was the use of medications that predominantly target fasting and preprandial glucose as discussed previously. Although both metformin and sulfonylurea formulations have some impact on reducing postprandial glucose excursions, they are not as effective as other medications, such as glitinides, α-glucosidase inhibitors, or glucagon-like peptide agonists, which are generally regarded as postprandial treatments. Use of these medications may have yielded more significant reductions in postprandial glucose and HbA1c levels given the relatively low baseline HbA1c (7.3 and 7.2% for the FP group and PP group, respectively). As demonstrated by Monnier and colleagues,[17] reducing postprandial glucose excursions is particularly effective in improving overall glycemia when HbA1c levels are <7.3%.

Further, because this was a behavioral study conducted at a single site using individual randomization, there is a risk that less intensively managed subjects may be influenced by contact with more intensively managed subjects. This contamination can dilute the apparent benefit of the intervention if these subjects choose to adopt the more rigorous behavior. A multicenter design with cluster randomization would eliminate this risk, as shown by Klonoff and colleagues.[18]

Despite these limitations, results from our study are clinically relevant because of the close association among CIMT, postprandial hyperglycemia, and the development of vascular disease. Epidemiological studies have shown a strong association between postmeal and postprandial glycemia and cardiovascular risk and outcomes in diabetic and nondiabetic populations.[6–8,19] A growing body of evidence also shows a causal relationship among postmeal hyperglycemia and oxidative stress,[20] CIMT,[21] and endothelial dysfunction,[22,23] all of which are known markers of cardiovascular disease. O'Leary and colleagues[5] demonstrated that increases in CIMT, as measured noninvasively by ultrasonography, are directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease. In a more recent study, Ravikumar and colleagues[24] showed that increases in CIMT strongly correlate with decreased flow-mediated dilation, the vasodilatory response of a vessel to elevations in blood flow-associated shear stress, which may play a role in the pathogenesis of vascular disease.[25]

In summary, it was shown that using postprandial SMBG results to guide therapy has a positive effect on cardiovascular risk and overall glycemic control in noninsulin-treated T2DM subjects. Additional studies are needed to expand our understanding of the value and utility of SMBG use in various diabetic populations.

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