Empirically Establishing Blood Glucose Targets to Achieve HbA_{1c} Goals

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To determine the average fasting, postprandial, and bedtime self-monitored blood glucose (SMBG) concentrations associated with specified HbA_{1c} levels using data from the A1c-Derived Average Glucose (ADAG) study.

RESEARCH DESIGN AND METHODS

The ADAG study was a multicenter observational study that used continuous glucose monitoring and SMBG testing to determine the relationship between mean average glucose and HbA_{1c}. We used the SMBG data from 470 of the ADAG study participants (237 with type 1 diabetes and 147 with type 2 diabetes) to determine the average fasting, premeal, 90-min postmeal, and bedtime blood glucose (BG) for predefined target HbA_{1c} groups between 5.5 and 8.5% (37–69 mmol/mol). *t* Tests were used to compare mean BG values between type 1 and type 2 diabetes groups.

RESULTS

The average fasting BG needed to achieve predefined HbA_{1c} target levels of 5.5–6.49% (37–47 mmol/mol), 6.5–6.99% (48–52 mmol/mol), 7.0–7.49% (52–58 mmol/mol), 7.5–7.99% (58–64 mmol/mol), and 8.0–8.5% (64–69 mmol/mol) were 122 mg/dL with 95% CI 117–127, 142 mg/dL (135–150), 152 mg/dL (143–162), 167 mg/dL (157–177), and 178 mg/dL (164–192), respectively. Postmeal BG to achieve the HbA_{1c} level of 6.5–6.99% (48–52 mmol/mol) and 7.0–7.49% (52–58 mmol/mol) were 139 mg/dL (134–144) and 152 mg/dL (147–157), respectively. Bedtime BG was 153 mg/dL (145–161) and 177 mg/dL (166–188), respectively.

CONCLUSIONS

We have determined the average BG at premeal, postmeal, and bedtime to achieve a variety of HbA_{1c} targets. These results, based on empirical data, will help patients and providers set realistic day-to-day SMBG targets to achieve individualized HbA_{1c} goals.

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Recent diabetes management guidelines specify that treatment goals should be individualized based on age, comorbidities, and duration of disease, with an American Diabetes Association (ADA)/European Association for the Study of Diabetes goal of <7% (<53 mmol/mol) or American Association of Clinical Endocrinologists (AACE) goal of ≤6.5% (≤48 mmol/mol) in otherwise healthy patients (1,2). Although HbA_{1c} is the target, it is measured once every 3 months, and day-to-day self-management of diabetes to achieve and maintain the individualized target HbA_{1c} is facilitated by self-monitored blood glucose (SMBG) values, especially in patients treated with insulin (1–4). To achieve the recommended HbA_{1c} goals, the ADA, the European Association for the Study of Diabetes, the AACE, and the International Diabetes Federation (IDF) have recommend SMBG targets (Table 1), the origins of which are obscure but appear to be based predominantly on expert opinion (1–5). As a result, there is wide variation in the recommended SMBG targets to achieve a HbA_{1c} <7% (<53 mmol/mol) and little to guide clinicians and patients on how to achieve other, individualized, targets.

We sought to determine the average fasting, postprandial, and bedtime glucose values, based on empirical data, to achieve and maintain target HbA_{1c} levels in the outpatient setting.

RESEARCH DESIGN AND METHODS

We analyzed blood glucose (BG) data from the A1c-Derived Average Glucose (ADAG) study, which was conducted to establish the relationship between average glucose concentrations and HbA_{1c} levels (6). The details of the ADAG study have been published previously. In brief, the ADAG study cohort consisted of 507 nonpregnant adult individuals between 18 and 70 years old with stable HbA_{1c} values for 3 months from 10 international centers: U.S. (6), Europe (3), and Africa (1). There were 268 with type 1 diabetes, 159 with type 2 diabetes, and 80 without diabetes. During the 12-week study period, HbA_{1c} was measured monthly, and continuous glucose monitoring (CGM) (Medtronic MiniMed, Northridge, CA) was performed at baseline and three times at 4-week intervals for at least a 48 h period, with glucose levels assessed every 5 min. Participants were asked to perform 8-point SMBG profiles (preprandial, 90-min postprandial, bedtime, and 3:00 A.M.) with a HemoCue Glucose 201+ meter (HemoCue, Angelholm, Sweden) during CGM. All analyzed glucose values were plasma equivalents. Participants measured premeal and postmeal glucose concentrations with a HemoCue device that was regularly calibrated and checked for correct time and date. The prebreakfast HemoCue glucose was considered the fasting value. Premeal glucose levels included any glucose designated before a meal. Glucose levels were not specifically flagged as at bedtime on the HemoCue device, so we chose any unflagged HemoCue value between 8:00 P.M. and 12:00 A.M. as a surrogate for bedtime BG. Although we had access to CGM and LifeScan SMBG data, timing of meals was not indicated for these methods, and therefore they were not used to determine periprandial glucose measurements.

We performed the current analyses on 378 of the originally published cohort (237 type 1 diabetes patients, representing 88% of the original ADAG study cohort, and 141 type 2 diabetes patients, 89% of original cohort). They were selected based on having HbA_{1c} values at 3 months between 5.5 and 8.5% (37–69 mmol/mol). These subjects had a total of 30,108 HemoCue BG values (4,031 fasting, 12,943 before meal, 12,602 90 min after a meal, and 4,563 at bedtime) monitored over an average of 11 days per participant during the 12-week study period. There were, on average, 9 fasting, 28 premeal (including fasting), 27 postmeal, and 7 bedtime HemoCue (SMBG) values for each subject.

We calculated the mean fasting, premeal, postmeal, and bedtime BG for each participant. For each HbA_{1c} group of 5.5–6.49% (37–47 mmol/mol), 6.5–6.99% (48–52 mmol/mol), 7.0–7.49% (52–58 mmol/mol), 7.5–7.99% (58–64 mmol/mol), and 8.0–8.5% (64–69 mmol/mol), the mean fasting, premeal, postmeal, and bedtime BG of the participants within the group were averaged. The mean premeal, postmeal, and bedtime BG were compared between type 1 and type 2 diabetes patients using *t* tests.

All analyses were performed with SAS version 9.3. The protocol was approved by the Partners Healthcare Institutional Review Board.

RESULTS

Mean fasting, premeal, 90-min postmeal, and bedtime BG in each HbA_{1c} group of 5.5–6.49% (37–47 mmol/mol), 6.5–6.99% (48–52 mmol/mol), 7.0–7.49% (52–58 mmol/mol), 7.5–7.99% (58–64 mmol/mol), and 8.0–8.5% (64–69 mmol/mol) are summarized in Table 2. There was no difference in mean fasting BG between type 1 and type 2 diabetes within the same HbA_{1c} group. Type 1 diabetes patients had higher average premeal BG compared with type 2 diabetes patients in the HbA_{1c} 7.0–7.49% (52–58 mmol/mol) group (BG 156 vs. 144 mg/dL; $P = 0.01$) and the HbA_{1c} 7.5–7.99% (58–64 mmol/mol) group (BG 159 vs. 141 mg/dL; $P = 0.01$). Conversely, patients with type 2 diabetes in the highest HbA_{1c} group, 8.0–8.5% (64–69 mmol/mol), had a significantly higher postmeal BG of 241 vs. 197 mg/dL ($P = 0.02$) compared with the type 1 diabetes patients.

There were significant differences in mean premeal and postmeal BG between specified breakfast, lunch, and supper meals, with the average

Table 1—Summary of current SMBG targets

	ADA (1)	AACE (2)	IDF-Europe type 1 (3)	IDF type 2 (4)
HbA_{1c}, % (mmol/mol)	<7 (<53)*	≤6.5 (≤48)*	6.2–7.5 (44–58)	<7 (53)*
Premeal, mg/dL	70–130*	<110*	91–120	<115
Postmeal, mg/dL	<180*	<140*	136–160	<160
Before bedtime, mg/dL			110–135	

*HbA_{1c} goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

Table 2—Average glucose levels (95% CI) for specified HbA_{1c} levels

	HbA_{1c} group, % (mmol/mol)				
	5.5–6.49 (37–47)	6.5–6.99 (47–53)	7.0–7.49 (53–58)	7.5–7.99 (58–64)	8.0–8.5 (64–69)
	Estimated average glucose, mg/dL				
	111–139	140–153	154–168	169–182	183–197
All diabetes	*n* = 119	*n* = 91	*n* = 74	*n* = 61	*n* = 33
Mean fasting, mg/dL	122 (117–127)	142 (135–150)	152 (143–162)	167 (157–177)	178 (164–192)
Mean premeal*, mg/dL	118 (115–121)	139 (134–144)	152 (147–157)	155 (148–161)	179 (167–191)
Mean postmeal, mg/dL	144 (139–148)	164 (159–169)	176 (170–183)	189 (180–197)	206 (195–217)
Mean bedtime, mg/dL	136 (131–141)	153 (145–161)	177 (166–188)	175 (163–188)	222 (197–248)
Type 1 diabetes	*n* = 53	*n* = 64	*n* = 47	*n* = 47	*n* = 26
Mean fasting, mg/dL	122 (113–132)	144 (134–154)	155 (143–168)	170 (159–181)	178 (161–194)
Mean premeal*, mg/dL	119 (115–124)	140 (134–147)	156 (150–163)	159 (151–166)	175 (162–188)
Mean postmeal, mg/dL	139 (133–145)	161 (155–168)	175 (167–183)	190 (180–199)	197 (188–205)
Mean bedtime, mg/dL	140 (132–148)	154 (144–164)	180 (164–195)	179 (166–193)	214 (189–240)
Type 2 diabetes	*n* = 66	*n* = 27	*n* = 27	*n* = 14	*n* = 7
Mean fasting, mg/dL	122 (118–127)	139 (139–147)	147 (133–161)	157 (139–176)	179 (158–201)
Mean premeal*, mg/dL	118 (113–122)	137 (130–145)	144 (137–151)	141 (131–151)	196 (168–224)
Mean postmeal, mg/dL	147 (141–153)	170 (163–177)	175 (165–186)	185 (163–206)	241 (214–268)
Mean bedtime, mg/dL	133 (126–140)	151 (139–162)	173 (161–184)	162 (133–190)	259 (177–341)

*Includes fasting values.

prelunch BG significantly lower than the prebreakfast and supper averages in patients in the prespecified HbA_{1c} groups (Table 3). The average postbreakfast BG was significantly higher than the postlunch and supper averages across nearly all HbA_{1c} groups analyzed.

CONCLUSIONS

Since the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study established the importance of glycemic control to ameliorate diabetes-related complications, great effort has been expended to achieve the HbA_{1c} targets that proved effective in those studies. With the publication of the DCCT results in 1993, recommendations for SMBG targets were based largely on the DCCT protocol in which SMBG targets were 70–120 mg/dL preprandial and <180 mg/dL postprandial (7,8). The provenance of the specified target glucose levels is unclear. Currently recommended SMBG targets appear to be largely based on expert opinion or from extrapolations from regression equations comparing the mean of all the daily capillary-measured plasma glucose levels, independent of the distribution during the day, and HbA_{1c}.

We sought to determine the average SMBG values for a range of stable HbA_{1c} targets of 5.5–8.5% (37–69 mmol/mol) and found that the currently published SMBG targets are not consistent with the empirical data. For example, in contrast with the published premeal BG targets (Table 1), where most organizations have recommended premeal/fasting BG <110–115 mg/dL, the results from the ADAG study revealed that patients achieving HbA_{1c} 5.5–6.49% (37–47 mmol/mol) had a mean premeal BG of 122 mg/dL (95% CI 117–127) and those with HbA_{1c} 6.5–6.99% (48–52 mmol/mol) had a mean premeal BG of 142 mg/dL (95% CI 135–150). The postprandial BG levels derived from the ADAG study data were more in-line with the published guidelines; however, where the recommended targets are often "less than 180 mg/dL," we have been able to quantify the actual values (~150 mg/dL) that will result in HbA_{1c} levels <7% (<53 mmol/mol).

Table 3—Average glucose levels (mg/dL) (95% CI) before and after meals for specified HbA_{1c} levels

	HbA_{1c} group, % (mmol/mol)				
	5.5–6.49 (37–47)	6.5–6.99 (48–52)	7.0–7.49 (52–58)	7.5–7.99 (58–64)	8.0–8.5 (64–69)
	Estimated average glucose, mg/dL				
	111–139	140–153	154–168	169–182	183–197
Prebreakfast	122 (117–127)	142 (135–150)	152 (143–162)	167 (157–177)	178 (164–192)
Prelunch	113 (108–117)*	127 (121–133)*	147 (139–155)	140 (132–149)*	167 (151–182)
Presupper	119 (115–123)	145 (138–152)	155 (148–162)	163 (153–173)	186 (168–205)
Postbreakfast	150 (144–157)†	177 (170–184)†	192(181–203)†	206 (193–219)†	219 (204–234)‡
Postlunch	140 (135–145)	158 (151–164)	172 (164–180)	181 (170–191)	194 (178–209)
Postsupper	142 (136–146)	159 (152–166)	169 (162–177)	182 (171–193)	211 (195–227)

*$P < 0.05$ comparing mean prelunch glucose to prebreakfast and presupper. †$P < 0.05$ comparing mean postbreakfast glucose to postlunch and postsupper. ‡$P < 0.05$ comparing mean postbreakfast glucose to postlunch.

The consequences of using the previously published, nonempirical data may include pushing patients harder to achieve lower fasting levels than are actually required. Considering the safety concerns surrounding hypoglycemia, in particular, nocturnal hypoglycemia and hypoglycemia unawareness, the current recommended glucose targets emphasizing lower fasting BG and higher postprandial BG should be re-evaluated. The target BG levels necessary to achieve specified HbA_{1c} values were generally similar for type 1 and type 2 diabetes patients (Table 2), endorsing a similar set of target values regardless of type of diabetes in nonpregnant adults. While there were statistically significant differences between prelunch and postbreakfast BG averages compared with other meals within an HbA_{1c} group, clinically these differences are small (<15% difference within an HbA_{1c} group), and it would be reasonable to apply the aggregate premeal and aggregate postmeal BG values for all meals.

A strength of the ADAG study in addressing BG targets is that it included people with a wide range of stable HbA_{1c} values from many different communities. Although the BG measurements over the course of the 12-week study were measured in a structured way (before meals and 2 h after meals), the timing of measurements was dictated by the participants real-life environment and schedule. Both a strength and a limitation of this study is that the BG measurements were obtained with a laboratory-quality point-of-care glucose monitoring device, which may give somewhat more precise and accurate BG measurements than usual consumer SMBG devices, something that will need to be accounted for when extrapolating these results to clinical practice. The relatively small numbers of type 2 diabetes patients, especially at the higher HbA_{1c} ranges, resulted in larger CIs for this subgroup, but with the exception of postprandial mean BG in the highest HbA_{1c} target range of 8.0–8.5%, the mean values between type 1 and type 2 diabetes patients were similar (<15% difference within an HbA_{1c} group), and we chose to present the aggregate data. Another potential limitation is that we did not account for differences in treatment regimens, but our focus was on determining the achieved mean BG for a given stable HbA_{1c} regardless of treatment regimen.

The choice of glucose monitoring schedule and goals remains complex, predicated on target HbA_{1c}, treatment regimens, risk of hypoglycemia, and cost-effectiveness. For patients and providers, setting appropriate day-to-day BG testing goals to achieve a specific and individualized HbA_{1c} target is important to guide the patient's self-care and self-management. The current study establishes realistic target BG levels, based on empirical data, to inform our patient-centered care. We hope that these data will be used by professional societies, clinicians, and patients to guide the appropriate choice of glucose targets and treatment to achieve their individualized HbA_{1c} goal.

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References

1. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013;36(Suppl. 1):S11–S66
2. Handelsman Y, Mechanick JI, Blonde L, et al.; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011; 17(Suppl. 2):1–53
3. International Diabetes Federation (European Region). A Desktop Guide to Type 1 (Insulin-Dependent Diabetes) [Internet], 1998. Available from http://www.staff.ncl.ac.uk/philip.home/t1dg1998.htm. Accessed 20 December 2013
4. IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels, International Diabetes Federation [Internet], 2012. Available from http://www.idf.org. Accessed 20 December 2013
5. Rydén L, Standl E, Bartnik M, et al.; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. Eur Heart J 2007;28:88–136
6. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1C-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31: 1473–1478
7. Weir GC, Nathan DM, Singer DE. Standards of care for diabetes. Diabetes Care 1994;17: 1514–1522
8. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med 1993;328: 1676–1685