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ADAG Study Group Data Links A1C Levels with Empirically Measured Blood Glucose Values - New Treatment Guidelines Will Now be Needed

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A new analysis of the ADAG (A1C-derived average glucose) Study Group report that was published in 2008 empirically links target blood glucose values with A1C levels.[1] This is a major advance for clinicians who will now be able to assign target self-monitored blood glucose values according to patients' intended levels of glycemia as measured by A1C levels. The fasting and postprandial blood glucose levels needed to achieve A1C levels under 7% might surprise many clinicians and may lead professional diabetes associations to develop new guidelines.

The Original ADAG Study

An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in nonpregnant individuals.[2] The group concluded that "the A1C assay provides a reliable measure of chronic glycemia and correlates well with the risk of long-term diabetes complications." The same year an international multicenter study by the ADAG Study Group reported the relationship between average glucose and A1C levels to estimate the relationship between the two metrics.[3] This group derived a mathematical relationship using a combination of continuous glucose monitoring and frequent fingerstick capillary blood glucose testing.

The ADAG investigators studied 507 subjects (including 268 subjects with type 1 diabetes, 159 subjects with type 2 diabetes, and 80 subjects without diabetes) from 10 international centers. A1C levels obtained at the end of a 3-month study period were compared with calculated average glucose (AG) levels measured over this 3-month period. AG levels were calculated by combining weighted results from at least 2 days of continuous glucose monitoring performed 4 times, with 7-point daily self-monitoring of capillary (fingerstick) glucose performed at least 3 days per week. Using linear regression analysis, the relationship between the A1C level at the end of the 3-month study period and the calculated AG during the preceding 3 months best fit an equation of estimated $AG_{mg/dl} = (28.7 \times A1C) - 46.7$ and estimated $AG_{mmol/l} = (1.59 \times A1C) - 2.59$ with $R^2 = .84$ and $P < .0001$. The relationship between A1C and estimated AG was the same when only the subjects with diabetes were included, and the linear regression equations also did not differ significantly across subgroups based on diabetes type, age, gender, race/ethnicity, or smoking status.[3]

There was no international standard for A1C from the time frame that commercial assays for this analyte were developed in the 1980s through the end of the DCCT study in the early 1990s.[4] During the late 1990s and early 2000s the International Federation for Clinical Chemistry (IFCC) developed a new international reference method for A1C.[5-6] This assay was described as more specific and therefore superior to the A1C assays that were then used in the United States, Sweden, and Japan.[6] In 2007, IFCC recommended that their assay be deemed as the international standard for A1C testing and it should be accompanied by new units for reporting A1C values.[7] IFCC recommended that test results be reported to clinicians in SI units as mmol/mol instead of in conventional units as percentages.[8] That same year to harmonize A1C assays between the United States and Europe a joint statement was crafted by the American Diabetes Association, the European Association for the Study of Diabetes, the International Diabetes Federation, and the IFCC. This statement stipulated that A1C results should be reported worldwide in (1) IFCC units (mmol/mol), (2) IFCC-derived NGSP units (%) using an IFCC-NGSP master

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Table 1. Estimated Average Glucose (eAG) Compared to Measured Hemoglobin A1c Levels.

Hemoglobin A1c	eAG in mg/dl[a]	eAG in mmol/l[b]
5	97 (76-120)	5.4 (4.2-6.7)
6	126 (100-152)	7.0 (5.5-8.5)
7	154 (123-185)	8.6 (6.8-10.3)
8	183 (147-217)	10.2 (8.1-12.1)
9	212 (170-249)	11.8 (9.4-13.9)
10	240 (193-282)	13.4 (10.7-15.7)
11	269 (217-314)	14.9 (12.0-17.5)
12	298 (240-347)	16.5 (13.3-19.3)

Values in parentheses are 95% confidence intervals.
[a]Linear regression eAG (mg/dl) = 28.7 × A1C − 46.7.
[b]Linear regression eAG (mmol/l) = 1.5944 × A1C − 2.5944.
Source: Adapted from Nathan et al.[3]

equation to convert one measurement to the other, and (3) an A1C-derived average glucose (ADAG) value calculated from the A1C result as an interpretation of the A1C results.[7] The ADAG report by Nathan and colleagues was published later in 2008.[3]

The Derivation of the Estimated Average Glucose (eAG)

The derivation of eAG served two purposes. First, the creation of the eAG metric permitted clinical chemists from the United States and Europe to use the same metric for mean glycemia without either group having to recalibrate or change their normal value ranges. Second, the eAG served as a clinical tool to present mean glycemia to patients. The A1C served as an anchor from which the eAG was derived and compared to.[9] The translation of A1C to eAG based on the linear regression is shown in Table 1, for conventional and SI units.[3]

After the first report from the ADAG group, many clinicians assumed that a benefit of the eAG metric was that mean glycemia results would then be reported in units that would be considered more understandable and meaningful to patients than the more abstract units of percentage of glycated hemoglobin. I have never found eAG to be a useful concept for teaching patients how to interpret their self-monitored or laboratory blood glucose values. Patients are taught to measure fasting, premeal, postmeal, and bedtime glucose levels. There is no generally used simple formula for converting these types of values into an estimated average glucose level throughout the day. eAG was calculated by combining weighted results over 3 months from at least 2 days of continuous glucose monitoring performed 4 times, with 7-point daily self-monitoring of fingerstick SMBG testing performed at least 3 days per week.[3] eAG is not the same as mean BG as calculated by glucose values collected by SMBG or by continuous glucose monitoring (CGM). In a comparison of eAG and mean BG calculated from the average of self-monitored blood glucose (SMBG) levels captured by a monitor, the eAG over- or underestimated eAG by 28.7 mg/dl or greater (HbA1c difference of 1% or greater) in approximately 33% of patients from 2 populations.[10] Furthermore, with the use of continuous glucose monitoring, it turns out that mean glucose as measured by CGM is also not necessarily the same as the eAG level because the latter is based on particular time points derived in part from 7-point testing whereas CGM measures all points throughout the day. In a series of 244 subjects undergoing nearly continuous glucose monitoring for 3 months the mean and median absolute difference sensor glucose concentrations differed from the value calculated using the regression equation by 14.3 mg/dl and 10.1 mg/dl, respectively.[11] In my experience, eAG has not been widely adopted as a substitute for other metrics of mean glycemia, such as A1C, which is the very number eAG, was intended to substitute for.

Reanalysis of ADAG Data

On February 10, 2014, Nancy Wei, Hui Zheng, and David Nathan published a brilliant article reanalyzing the ADAG data and creating a valuable set of metrics for assessing glycemia.[1] Instead of combining all the ADAG group's 7-point SMBG and CGM data into a single data point to describe one single estimated average glucose level over an entire day, this article used only the BG values collected by SMBG where they could assign a meal-related time (ie, fasting, preprandial × 3, postprandial × 3, and bedtime) to a data point. The prebreakfast glucose value was considered the fasting value. The authors calculated the average glucose concentrations for each of these 7 times of day associated with specified ranges of A1C values achieved by subjects in the ADAG study.

The authors used the SMBG data from 378 of the 427 ADAG study participants (237 with type 1 diabetes and 141 with type 2 diabetes) whose A1C at the end of 3 months of observation was 5.5-8.5%. They calculated the average fasting, preprandial, postprandial, and bedtime blood glucose values for 5 subsets from subjects' predefined target HbA1c between 5.5 and 8.5%. The subsets were 5.5-6.49%, 6.5-6.99%, 7.0-7.49%, 7.5-7.99%, and 8.0-8.5% (Table 2).

To my knowledge this article is the first study to ever to ever present detailed empiric SMBG values throughout the day associated with A1C outcomes. These results will help patients and providers set realistic day-to-day SMBG targets to achieve individualized HbA1c goals. The benefit of this information is enormous. Health care professionals will now have access to data about what types of glucose levels, as measured by SMBG, are associated with various intended A1C levels.

Table 2. Mean Blood Glucose Levels for Bins of Specified Hemoglobin A1c Levels.

	Blood glucose (mg/dl with 95% confidence interval)				
	Hemoglobin A1c (%)				
	5.5-6.49 (n = 119)	6.5-6.99 (n = 91)	7.0-7.49 (n = 74)	7.5-7.99 (n = 61)	8.0-8.5 (n = 33)
Mean fasting	122 (117-127)	142 (135-150)	152 (143-162)	167 (157-177)	178 (164-192)
Mean premeal	118 (115-121)	139 (134-144)	152 (147-157)	155 (148-161)	179 (167-191)
Mean postmeal	144 (139-148)	164 (159-169)	176 (170-183)	189 (180-197)	206 (195-217)
Mean bedtime	136 (131-141)	153 (145-161)	177 (166-188)	175 (163-188)	222 (197-248)

Source: Adapted from Wei et al.[1]

Table 3. Current A1C and Blood Glucose Targets by 4 Major Associations.

	ADA	AACE	IDF Europe Type 1	IDF Type 2
A1C (%)	<7[a]	<6.5[a]	6.2-7.5	<7[a]
Premeal (mg/dl)	70-130[a]	<110[a]	91-120	<115
Postmeal (mg/dl)	<180[a]	<140[a]	136-160	<160
Bedtime (mg/dl)			110-135	

Sources: Adapted from Wei et al,[1] American Diabetes Association,[12] Handelsman et al,[13] International Diabetes Federation European Region,[14] and International Diabetes Federation, 2012 Clinical Guidelines Task Force.[15]

[a]A1c 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.

Current Relationships Between Target Levels of Mean Glycemia and Target Blood Glucose Levels

The four most widely quoted blood glucose targets that have been proposed by professional organizations[12-15] to achieve target levels of mean glycemia (as measured by A1C) are mainly based on the opinions and experience of the developers (Table 3). There has not been a prior published guideline based on the type of data presented in this article, which links BG levels at various well characterized times of day with mean glycemia as reflected by A1C levels.

Misalignment Between Current Target Levels of Mean Glycemia and Target Blood Glucose Levels

This reanalysis of ADAG data has demonstrated that current blood glucose target levels are not properly aligned with target levels of mean glycemia as defined by normal or near-normal levels of A1C. The fasting target BG levels are too low for the four major organizations' guidelines of glycemic targets and the postprandial target BG levels are also too low for 3 of these 4 guidelines.[12-15]

Many patients are encouraged to get their BG levels down low enough to attain a normal (or not frankly abnormal) A1C level of 5.6-6.49%, which is the bin containing the lowest range of A1C levels studied in this ADAG article. The fasting blood glucose levels attained by the subjects with these levels of mean glycemia tended to be higher than the maximum levels that were recommended in most guidelines. The ADAG subjects whose A1C levels were in this range were found to have mean fasting blood glucose levels of 122 mg/dl for both type 1 and type 2 patients. This mean value is (1) above the top of the target range (<110 mg/dl) established by the American Association of Clinical Endocrinologists (AACE) in 2011, (2) above the top of target range (91-120 mg/dl) established for type 1 diabetes by the International Diabetes Federation (IDF) European Region in 1998, (3) above the top of the target range (<115 mg/dl) established for type 2 diabetes by the IDF in 2012, and (4) toward the high end of the target range (70-130 mg/dl) established by the American Diabetes Association (ADA) as of this year.[12-15]

Other patients are encouraged to bring their A1C down to a near-normal range as low as 6.5-6.99% which is within the target range for A1C set by the ADA guideline and the IDF Type 2 guideline (Table 2). For subjects with A1C levels in this range, the ADAG study showed mean fasting blood glucose levels of 142 mg/dl. For these subjects the fasting glucose levels were clearly higher than the fasting BG targets specified by the ADA (70-130 mg/dl)[12] and IDF Type 2 (115 mg/dl).[15]

The observed self-monitored postprandial blood glucose values in the ADAG study were also not well aligned with target levels of mean glycemia recommended by 3 of the 4 major guidelines: The measured mean postprandial blood glucose levels attained by the ADAG subjects were higher than permitted (based on A1C levels) by AACE, IDF Europe Type 1, and IDF Type 2. The AACE guideline specifies that the maximum recommended A1C level is 6.5%, and the target postprandial BG is below 140 mg/dl. In the ADAG population the mean postprandial BG for subjects with acceptable A1C values of 5.6-6.49 was 144 mg/dl, indicating that most of the postprandial BG values were above the AACE target. The IDF Europe type 1 guideline recommends a maximum A1C of 7.5% and a maximum postprandial glucose level of 136-160 mg/dl. Type 1 ADAG subjects with A1C values of 6.5-6.99% and 7.0-7.49% had mean postprandial BG levels, respectively, of 161 and 175 mg/dl. Thus, most subjects with A1C values of 6.5-7.49% whose mean glycemic levels were by definition within the IDF Europe type 1 target range had postprandial BG values above the recommended range. With the IDF type 2 guideline, the recommended postprandial BG levels and target A1C levels were also misaligned. This

guideline recommends a maximum A1C of 7% and a maximum postprandial glucose level of 136-160 mg/dl. Type 2 ADAG subjects with A1C levels of 6.5-6.99% had mean postprandial glucose levels of 170 mg/dl indicating that most of their postprandial BG values were above target. The observed mean postprandial BG level was within the target range for both IDF guidelines in ADAG subjects with A1C levels of 5.6-6.49%. The ADA target postprandial BG is the highest of the 4 guidelines at <180 mg/dl. The mean postprandial blood glucose levels for subjects with A1C levels of 5.6-6.49% and 6.5-6.99% were, respectively, 144 and 164 mg/dl, which means that for this guideline, the target A1c levels and the observed mean postprandial blood glucose levels were appropriately aligned.

Conclusions About Blood Glucose Targets

Currently published guidelines present target fasting blood glucose levels measured by SMBG that are intended to achieve normal mean levels of glycemia. The 2014 ADAG data demonstrate that: (1) target SMBG levels in major guidelines are not consistent with empirical data to achieve normal or near-normal mean glycemia; (2) fasting SMBG target levels can be safely raised by guidelines to diminish the risk of treatment-induced hypoglycemia and yet still achieve normal and near-normal mean glycemia as measured by A1C levels; and (3) most postprandial target SMBG target levels should be raised (in 3 of the 4 major guidelines) to establish alignment between intended levels of mean glycemia and observed levels of blood glucose.

It is not possible to conclude from this data set that the magnitude of the rise in blood glucose between preprandial and postprandial levels correlates with worsening control. This is because the delta between mean premeal and postmeal blood glucose levels in the lowest A1C subjects (5.5-6.49%) was 26 mg/dl and for the highest A1C subjects (8-8.5%) this delta was 27 mg/dl.

The Wei et al[1] article provides realistic BG targets for various levels of control. For some patients with hypoglycemia unawareness or severe vascular disease, the best goal is an A1C of greater than 7.0%.[16] The aforementioned association guidelines are intended for a goal of excellent control and presumably aim for BG levels to achieve A1C levels of below 6.5-7%. These guidelines, however, offer no recommendations for what levels of fasting and postprandial glycemia are needed for patients whose target A1C is even higher, but the recent ADAG article provides this type of data.[1]

SMBG has the best outcomes when this procedure is performed as part of a structured BG testing program.[17-18] Until now, it has not been clear what types of glucose goals to set. Based on the Wei et al article,[1] there are specific BG targets that can now be chosen in anticipation of achieving selected levels of A1C.

Where Targeted BG Monitoring Is Headed

I expect that other empirically collected data sets will become available in the near future with their own mean fasting and postprandial BG levels. We will be able to see whether the diversely constructed ADAG population data apply to all populations. We will also learn whether specific populations with unique glycosylation characteristics have unique BG levels that should be targeted for various levels of intended mean glycemia as defined by A1C. The result will be development of future rational evidence-based guidelines for the entire population of diabetes patients as well as for subsets of patients that will recommend target levels of blood glucose control based on actual levels of A1C. The practice of SMBG has become more important than ever because for the first time there is now excellent evidence presenting which levels of blood glucose are needed to achieve intended levels of mean glycemia.

Abbreviations

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; ADAG, A1C-derived average glucose; AG, average glucose; eAG, estimated average glucose; CGM, continuous glucose monitoring; IDF, International Diabetes Federation; IFCC, International Federation for Clinical Chemistry; SMBG, self-monitored blood glucose

Declaration of Conflicting Interests

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