Shortfalls of the use of HbA1C-derived eAG in older adults with diabetes

Running title:

HbA1C-derived eAG in older adults

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Abstract

Aims: The haemoglobin HbA1C (HbA1C) value, translated into estimated average glucose concentration (eAG), is commonly used to assess glycaemic control and manage treatment regimens in people with diabetes. However, the relationships among HbA1C-derived eAG, and mean glucose concentration derived from continuous glucose monitoring (CGM) in different populations have not been well studied. We examined this relationship in older people with diabetes and compared the results to those currently used in clinical practice.

Methods: Data from 3 studies evaluating CGM in older adults (≥ 70 years of age), with stable glycaemic control were analysed retrospectively. Mean glucose and mean amplitude of glucose excursion (MAGE) were calculated from CGM data and correlated with HbA1C and HbA1C-derived eAG using the ADAG Study formula.

Results: HbA1C and CGM data were analysed from 90 patients with mean age 76 ± 5 years, HbA1C $7.9 \pm 1.2\%$ (63 ± 13 mmol/mol) and 77% with Type 2 diabetes. The HbA1C and HbA1C-derived eAG correlated significantly with CGM-measured mean glucose ($r^2 = 0.30$, $p < 0.00001$) and MAGE ($r^2 = 0.16$, $p = 0.00013$) in this population and all its subgroups, but the slopes of the relationship between HbA1C and eAG or CGM-measured mean glucose were significantly different.

Conclusions: HbA1C-derived eAG values may not accurately reflect CGM-measured mean glucose or MAGE in older adults with diabetes. Wide glucose excursions should be considered and HbA1C should be interpreted cautiously when making treatment changes based on HbA1C.

Keywords:

Diabetes, Older Adults, HbA1c, Estimated average glucose (eAG)

Introduction

Haemoglobin A1c (HbA1C) is commonly used as the gold standard test to assess long-term glycaemic control in the management of people with diabetes (1). The non-enzymatic, irreversible binding of circulating glucose with haemoglobin present in red blood cells (RBC) determines the level of HbA1C, which reflects average blood glucose levels over the previous 2-3 months based on RBC life span. Persistent high glucose levels reflected by high HbA1C levels have been associated with an increased risk of microvascular and macrovascular diseases (2, 3) . Lowering the HbA1C level decreases the risk of developing microvascular, and in some instances, macrovascular complications. Thus, HbA1C is widely used as an indicator of glycaemic control and as a target for treatment in patients with diabetes. Recently, the HbA1C-Derived Glucose (ADAG) study has shown a linear association between the measured average glucose concentrations and the HbA1C values in adults with Type 1 or Type 2 diabetes(4). Based on these findings, HbA1C values are now usually also reported as estimated average glucose (eAG) concentrations to provide a more recognized value for patients and providers to understand the level of glycaemic control. However, the ADAG study was performed in a selected population of adults, age 18-70, (mean age 46 ± 14 years) who had no hematologic or other known factors that would affect red cell lifespan or HbA1C measurements. Although the ADAG formula for eAG is applicable to an average population of people with Type 1 or Type 2 diabetes, it has not been validated in specific subgroups different from the original cohort, raising concerns about its generalizability to these populations (5) (6) (7) (8). Since the HbA1C value is now widely used as a therapeutic target and a quality measure for management of diabetes, there is an increased effort in clinical practice to achieve recommended HbA1C targets in all

patients. Although the standards of care in managing diabetes now recommend individualizing treatment regimens, HbA1C remains the most common test on which treatment decisions are based. This is particularly true for primary care practices which provide care for the majority of older adults with diabetes. If HbA1C-derived eAG does not reflect the true average glucose concentration in this population, it can increase the risk of overtreatment or under-treatment. This issue has prompted us to evaluate the relationship between HbA1C-derived eAG and actual mean glucose levels measured by continuous glucose monitoring (CGM) in older adults with Type 1 or Type 2 diabetes.

Materials and Methods

Data from 90 older adults (age >70 years) with Type 1 or Type 2 diabetes, who were participating in 3 clinical studies utilizing CGM glucose monitoring were combined and analysed. The titles of these studies were “Identifying and Overcoming Barriers to Diabetes Management in the Elderly: An Intervention Study(9), “Cardiac Autonomic Dysfunction in Older Adults with Diabetes” (manuscript in preparation), and “Simplification of diabetes regimen in elderly patients using glargine(10). These studies excluded patients with severe renal insufficiency (eGFR<20) or on dialysis, terminal illness limiting life expectancy to 12 months, or those living in supervised facilities. The CGM was performed in these trials to assess glucose excursions and unrecognized hypoglycaemia in older adults. All three trials used the iPro CGM device requiring finger-stick glucose readings 4 times a day for calibration. All three studies were approved by the institutional review board. For continuous glucose monitoring, the CGM System iPro™ (Medtronic Minimed, Inc.) was used to measure the interstitial glucose concentration at intervals of 5 minutes for ≥ 3 days while patients continued their usual daily activities. As required, patients also measured

finger-stick capillary glucose levels four times a day while wearing the CGM to calibrate the CGM system. The patients wore the CGM devices for 3-5 full days, with the average length of wear being 4.2 days, or 1,218 sensor readings. For the purpose of calculating CGM-derived mean glucose, only CGM sensor readings were used.

The HbA1C was drawn at the same time the CGM was inserted. As HbA1C is a measure of longer term glycaemic control, measurement of HbA1C before or after CGM would not be significantly different. We selected only those patients with stable HbA1C (value change $<0.5\%$ (5 mmol/mol)) as measured within 2-6 months prior to CGM, confirming stability of HbA1C. Thus, two consecutive HbA1C values were used to establish stability of the glycaemic control. The mean glucose levels were calculated based on CGM data. We also calculated mean amplitude of glycaemic excursions (MAGE) based on CGM. We chose MAGE as it is one of the most commonly used validated indices of glucose variability (11, 12) (13).

HbA1C was measured in the Joslin Clinical Laboratory using the HPLC ion capture method (Tosoh Medics, Inc. San Francisco, CA; reference range 20-40 mmol/mol (4.0-6.0%)) and eAG was calculated using the ADAG formula: $eAG\text{ (mg/dl)} = 28.7 \times \text{HbA1C} - 46.7$ (4)

Statistical Analysis

Data are presented as mean $\pm$ standard deviation and as n (%) for frequency data. CGM data were used to derive 1) mean glucose levels, and 2) indices of glucose excursions (MAGE). The Pearson correlation coefficient (r) was computed to evaluate the relationship between HbA1C and HbA1C-derived eAG and glucose parameters obtained from CGM (mean glucose and MAGE).

Results

Ninety older adults with diabetes who completed CGM studies and who qualified for this analysis were evaluated. (Table 1) The average age of the study population was 76 ± 5 years, average duration of diabetes was 24 ± 13 years and 77% had Type 2 diabetes. The majority of the population (84%) was Caucasian, and 59% were women. In our older cohort, 46% of patients had cardiovascular disease, 77% had hypertension, 77% had hypercholesterolemia, 11% had a history of stroke, 67% had neuropathy, 47% had difficulty with hearing, and 42% had difficulty with vision. We found 5% of our study cohort with severe anaemia (haemoglobin <10 g/dl) and 5% with severe uraemia (eGFR <30). Eighty nine patients were on insulin therapy and one patient was on insulin secretagogues. Both these classes of medications are known to have high risk of hypoglycaemic reactions in the older population. At baseline, the average HbA1C was $7.9\pm 1.2\%$ (63 ± 13 mmol/mol), CGM-based average mean glucose was 172 ± 37 mg/dL (9.48 ± 2 mmol/L), and average MAGE was 163 ± 46 mg/dL (9 ± 2.5 mmol/L).

We evaluated the correlation between the HbA1C values and the mean glucose concentration derived from CGM. As seen in **Figure 1**, there was a significant correlation between the HbA1C and CGM-derived mean glucose levels ($r^2=0.30$, $p<0.00001$, mean glucose= $17.19\times\text{HbA1C}+34.69$), but the slope of the relationship was significantly different than that derived from the ADAG Study data. Next, we evaluated whether HbA1C and CGM-derived mean glucose levels correlated differently in any of the patient subgroups by type of diabetes (Type 1 vs Type 2), number of insulin injections, or duration of the disease. As shown in **Table 1**, none of the groups showed a very close correlation between HbA1C or HbA1C-derived eAG and CGM-measured mean glucose levels. A comparison of the

regression equations within the multiple subgroups was also performed and is shown in **Table 2**. There were no significant differences in the slopes or intercepts for the regression equations for subgroup comparisons between HbA1C and mean glucose, except for the comparison between those subjects taking ≤ 2 insulin injections and > 2 insulin injections.

Next, we analysed the correlation between HbA1C and MAGE in all patients, as well as in all the subgroups described above. As seen in **Table 1 and Table 2**, the correlation between HbA1C and MAGE was further reduced ($r^2=0.15$, $p=0.00013$, $MAGE= 15.78 \times HbA1C + 39.04$) in all patients and in all of the subgroups with different types, duration and treatment modalities of diabetes. However, there was a significant difference in the slopes for the regression equations for the number of insulin injections ≤ 2 vs >2 per day in older adults.

Next we compared the slopes of the linear correlations between HbA1C and CGM-measured mean glucose in the older patient population and that generated from the ADAG study data. As shown in **Figure 2**, the two lines are significantly different, having the respective formulae of $eAG_{mg/dl} = 28.7 \times HbA1C - 46.7$ in the ADAG study and $mean\ glucose_{mg/dl} = 17.19 \times HbA1C + 34.69$ in the elderly population. The probability value comparing the two correlation coefficients is 0.0 indicating that the two correlation coefficients are significantly different from each other.

Discussion

In this study, we analysed the correlation between HbA1C and CGM-derived mean glucose in older adults with diabetes. Our analysis suggests that HbA1C, and consequently HbA1C-derived eAG, correlate less well and differently with mean

glucose calculated from CGM in a heterogeneous population of older adults with diabetes ($r^2=0.30$) compared to the data generated in the ADAG study ($r^2=0.84$) which did not include subjects over 70 years of age(4). As most laboratories are using the ADAG based formula to derive eAG from HbA1C, our results underscore possible shortfalls of using HbA1C and HbA1C-derived eAG as the sole parameters when making treatment decisions and individualizing therapies. In both our data and the ADAG data, the correlations between HbA1C and average glucose concentration derived by CGM are statistically significant, but the relationship is much tighter in the ADAG data, probably because of the much larger number of subjects and the mass of the data set. However, the calculated lines are significantly different as seen in Figure 2, and cross at an HbA1C of about 6.5% (48 mmol/mol). If these results are confirmed in a larger prospective study, it will be of clinical significance, as overestimation of eAG may result in overtreatment in this population if based solely on HbA1C levels, while underestimation may result in uncontrolled glucose levels. Although HbA1C reflects mean glucose concentrations over a longer duration than those derived from CGM measurements, the discrepancy between the 2 values is still important to consider at the time treatment decisions are made.

A recent CDC fact sheet published in 2014 notes that approximately 1 in 4 patients with diabetes (25.9%) are over the age of 65 years and the number is predicted to increase significantly in the next few decades (14). Studies that include the older population are few and those focused specifically on the aging population are rare. Thus, diabetes management in older adults involves extrapolating data from studies performed on younger adults. This fact remains true for studies such as the ADAG in which the average age of the study population was 46 ± 14 years. However, the interpretation of HbA1C and the calculations to derive eAG are

generally extrapolated and used in older adults. Other studies have raised similar concerns about eAG derived from HbA1C in different ethnic groups (6, 7).

Our results are consistent with recent observations suggesting decreased HbA1C specificity in an aging population (15, 16). These as well as the other studies assessing the impact of aging on HbA1C have shown higher values with increasing age. Our data, as shown in Figure 2, suggests that at lower HbA1C levels, calculated eAG is lower than mean glucose derived from CGM measurements, while at higher HbA1C levels, calculated eAG is higher than mean glucose measured by CGM. Discrepancy in these results is likely due to the impact of multiple variables that change HbA1C in opposite directions. This is an important observation as it reflects difficulties interpreting HbA1C in a heterogeneous, older population seen in primary care and endocrine clinics. Multiple confounders commonly seen with aging, such as uraemia and acidosis, carbamylation of haemoglobin, various types of anaemia, renal insufficiency and/or erythropoietin deficiency may either increase or decrease HbA1C levels in patients and sometimes coexist in the same patients making interpretation difficult(17-19). Thus, our analysis does not differentiate between the impacts of aging per se, versus the impact of comorbid conditions on HbA1C values, but rather looks at the difficulty in interpreting HbA1C as the sole parameter for making treatment decisions in the older population, which is heterogeneous and has multiple comorbidities. Although 5% of our cohort was found to have severe anaemia or uraemia, this small group did not affect the overall relationship between HbA1C and CGM-derived mean glucose. A larger study in this population with multiple chronic conditions is needed to further identify the impact of individual comorbidities.

In recent years, large prospective studies have shown that glycaemic control needs to be individualized, as tight control not only lacks benefits but can be harmful

in an older population and may increase morbidity and mortality (20) (21) (22). Thus, the reliability of HbA1C to reflect long term glycaemic control and its use to establish goals for diabetes management are even more critical in this population. The conversion of HbA1C into eAG has been generally successful in providing a better context for medical providers, as well as patients, to guide treatment modifications. However, as shown in this study, this correlation may not be the same in different populations.

In a previous study, we have shown that older adults have a high prevalence of hypoglycaemia and large glucose excursions, even with poor glycaemic control (23). Glucose excursions (glucose variability) have been shown to be an independent risk factor for complications from diabetes (24), cognitive impairment (25), and asymptomatic hypoglycaemia(26). The very poor correlation with MAGE shown in this study is consistent with our previous results and other published reports that suggest that HbA1C does not adequately reflect glucose excursions (13, 23, 27, 28). As shown in Table 2, older adults with a higher number of insulin injection also may have higher glucose excursions when compared to ≤ 2 insulin injections per day (10). These results are consistent with our previous study results suggesting lower frequency of hypoglycaemia and hyperglycaemia with simplified insulin regimens in older adults(10). This fact also needs wider reporting and acceptance by primary care providers, who manage the majority of older adults with diabetes.

Our results also demonstrate a subpopulation that may be at increased risk of harm from wide fluctuations in glucose, particularly hypoglycaemia. Older adults with Type 1 diabetes, with longer duration of the disease, and on multiple insulin injections may have worse correlation between HbA1C and mean glucose as well as

MAGE. This disparity is likely due to a higher number of large glucose excursions. On the other hand, patients with large glycaemic excursions could be prescribed complex insulin regimens. Consequently, HbA1C values should be interpreted with consideration of glucose excursion before making treatment changes in this population. The lack of significance in the subgroups are likely due to low numbers of patients in each group and suggest a need for larger studies in the heterogeneous older population.

In conclusion, our results indicate the need for caution in interpreting HbA1C results in older adults to avoid inappropriate treatment changes based solely on HbA1C values.

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Dr. Munshi is the guarantor of this work and, as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Standards of medical care in diabetes--2014. *Diabetes Care*. 2014;37 Suppl 1:S14-80.
2. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329(14):977-86.
3. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-12.
4. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473-8.
5. Cohen RM. A1C: does one size fit all? *Diabetes Care*. 2007;30(10):2756-8.
6. Wolffenbuttel BH, Herman WH, Gross JL, Dharmalingam M, Jiang HH, Hardin DS. Ethnic differences in glycemic markers in patients with type 2 diabetes. *Diabetes Care*. 2013;36(10):2931-6.
7. Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, Twombly JG, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med*. 2010;152(12):770-7.
8. Herman WH, Cohen RM. Hemoglobin A1c: teaching a new dog old tricks. *Ann Intern Med*. 2010;152(12):815-7.
9. Munshi MN, Segal AR, Suhl E, Ryan C, Sternthal A, Giusti J, et al. Assessment of barriers to improve diabetes management in older adults: a randomized controlled study. *Diabetes Care*. 2013;36(3):543-9.
10. Munshi MN SA, Ryan C, Slyne C, Saul N. Simplification of insulin regimens in older adults with diabetes decreases hypoglycemia, without worsening glycemic control. Scientific sessions of the American Diabetes Association. Chicago, IL; 2013:390P.
11. Service FJ. Glucose variability. *Diabetes*. 2013;62(5):1398-404.
12. DeVries JH. Glucose variability: where it is important and how to measure it. *Diabetes*. 2013;62(5):1405-8.
13. Kohnert KD, Augstein P, Heinke P, Zander E, Peterson K, Freyse EJ, et al. Chronic hyperglycemia but not glucose variability determines HbA1c levels in well-controlled patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2007;77(3):420-6.
14. CDC. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States. In: Services DoHaH, ed. Atlanta, GA US; 2014.
15. Dubowitz N, Xue W, Long Q, Ownby JG, Olson DE, Barb D, et al. Aging is associated with increased HbA levels, independently of glucose levels and insulin resistance, and also with decreased HbA diagnostic specificity. *Diabet Med*. 2014.
16. Pani LN, Korenda L, Meigs JB, Driver C, Chamany S, Fox CS, et al. Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. *Diabetes Care*. 2008;31(10):1991-6.

17. Nitin S. HbA1c and factors other than diabetes mellitus affecting it. *Singapore Med J.* 2010;51(8):616-22.
18. Sharif A, Baboolal K. Diagnostic application of the A(1c) assay in renal disease. *J Am Soc Nephrol.* 2010;21(3):383-5.
19. Brown JN, Kemp DW, Brice KR. Class effect of erythropoietin therapy on hemoglobin A(1c) in a patient with diabetes mellitus and chronic kidney disease not undergoing hemodialysis. *Pharmacotherapy.* 2009;29(4):468-72.
20. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.* 2011;10(11):969-77.
21. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-72.
22. Duckworth W, Abaira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360(2):129-39.
23. Munshi MN, Segal AR, Suhl E, Staum E, Desrochers L, Sternthal A, et al. Frequent hypoglycemia among elderly patients with poor glycemic control. *Arch Intern Med.* 2011;171(4):362-4.
24. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA.* 2006;295(14):1707-8.
25. Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, et al. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. *Diabetes Care.* 2010;33(10):2169-74.
26. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther.* 2011;13(8):813-8.
27. Fang FS, Li ZB, Li CL, Tian H, Li J, Cheng XL. Influence of glycemic variability on the HbA1c level in elderly male patients with type 2 diabetes. *Intern Med.* 2012;51(22):3109-13.
28. Sartore G, Chilelli NC, Burlina S, Di Stefano P, Piarulli F, Fedele D, et al. The importance of HbA1c and glucose variability in patients with type 1 and type 2 diabetes: outcome of continuous glucose monitoring (CGM). *Acta Diabetol.* 2012;49 Suppl 1:S153-60.

Table 1: Patient subgroups by age, number of insulin injections, and duration of diabetes.

Variables	Number	Mean HbA1C ¹ (%) (mmol/mol)	CGM ² - derived Mean	Mean eAG ³	Mean MAGE ⁴	HbA1C vs Mean Glucose (r ²)	HbA1C vs MAGE (r ²)
Type 1	20	8.3±0.8 (67±8.7)	182±23	193±23	202±42	0.005	0.008
Type 2	70	7.8±1.2 (62±13.1)	167±39	176±35	152±42	0.34	0.16
No. of insulin injections≤2	22	7.7±1.5 (61±16.4)	164±40	175±43	147±37	0.39	0.03
No. of insulin injections>2	68	8±1 (64±10.9)	173±35	182±29	169±47	0.26	0.25
Duration of diabetes≤10 years	11	7.7±1.7 (61±18.6)	157±39	174±49	143±52	0.62	0.08
Duration of diabetes >10 years	79	7.9±1.1 (63±12)	172±36	180±31	165±44	0.25	0.18

¹ Haemoglobin A1c

² Continuous glucose monitoring

³ Estimated average glucose

⁴ Mean amplitude of glucose excursions

Table 2: Comparison of intercept and slopes in different subpopulations in older adults

	Comparison	Difference in Slope ($\pm$ SE) ⁵	Difference in Intercept ($\pm$ SE)	p value
HbA1C⁶ vs Mean Glucose	Type 1 vs Type 2	-16.44 $\pm$ 9.02	22.82 $\pm$ 23.36	0.07
HbA1C vs Mean Glucose	Number of Insulin inj ≤ 2 vs > 2	-11.10 $\pm$ 5.18	34.09 $\pm$ 29.40	0.85
HbA1C vs Mean Glucose	Duration of diabetes ≤ 10 vs > 10	1.74 $\pm$ 6.54	40.83 $\pm$ 25.57	0.79
HbA1C vs MAGE⁷	Type 1 vs Type 2	-8.93 $\pm$ 11.98	46.92 $\pm$ 30.99	0.46
HbA1C vs MAGE	Number of Insulin inj ≤ 2 vs > 2	-21.39 $\pm$ 7.62	-19.62 $\pm$ 39.25	0.01
HbA1C vs MAGE	Duration of diabetes ≤ 10 vs > 10	-8.99 $\pm$ 9.21	27.05 $\pm$ 36.04	0.33

⁵ Standard error

⁶ Haemoglobin A1c

⁷ Mean amplitude of glucose excursions

Figure 1

Figure 2

Figure 1: Correlation between HbA1C and mean glucose (A) and HbA1C and MAGE (B)

Figure 2: Correlation between HbA1C vs mean glucose derived from CGM (dashed line) and HbA1C-derived eAG using the ADAG study formula (solid line).