PROFESSOR SANJOY PAUL (Orcid ID : 0000-0003-0848-7194)

Article type : Research Article

Title: Diabetic Medicine

Created by: Maria Davie

Email proofs to: rury.holman@dtu.ox.ac.uk

Article no.: DME-2016-00356

Article type: Research Article

Figures:2; Tables:4; Equations:0; References:35

Short title/Authors running head: • Paul and Holman

Research: Pathophysiology

Do glycoalbumin levels preferentially reflect changes in postprandial glucose excursions?

S. K. Paul^{1,2} and R. R. Holman³

¹Clinical Trials and Biostatistics Unit, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, and ²Melbourne EpiCentre, University of Melbourne and Melbourne Health, Melbourne, Victoria, Australia, and ³Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK

Accepted

Correspondence to: Rury R. Holman. E-mail: rury.holman@dtu.ox.ac.uk

What's new?

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/dme.13376](https://doi.org/10.1111/dme.13376)

This article is protected by copyright. All rights reserved

- Glycated albumin, which reflects prevailing blood glucose concentrations over the preceding 2–4 weeks, is considered as an alternative marker for glycaemic control in patients with diabetes that preferentially reflects postprandial glycaemia.
- Based on a small number of individuals, studies have reported association of glycated albumin and HbA_{1c} with pre- and postprandial glucose, without considering the inherent dynamic relationship between pre- and postprandial glucose levels.
- This study evaluated if glycated albumin better reflects the insulin-induced changes in postprandial glucose excursions seen in a large number of individuals with Type 2 diabetes in a long-term clinical trial setting.

Aims To evaluate whether plasma glycated albumin, which provides an integrated measure of plasma glucose levels over the preceding 2–4 weeks, better reflects changes in postprandial glucose excursions than HbA_{1c}.

Methods People with suboptimum glycaemic control on dual oral therapy were enrolled in the Treating-to-Target-in-Type 2 diabetes (4-T) trial, in which participants were randomized to the addition of once-daily basal insulin, twice-daily biphasic insulin or thrice-daily prandial insulin. Glycated albumin levels were assayed enzymatically from baseline and 1-year fasting plasma samples. We evaluated robust correlations of glycated albumin and HbA_{1c} both with fasting and postprandial glucose levels at these two time points, and with insulin-induced changes in the postprandial excursion.

Results Requisite data were available for 625 of the participants in the 4-T trial. Their mean ($\pm$ SD) age was 62 ± 10 years and body weight was 85.8 ± 15.9 kg, and their median (interquartile range) diabetes duration was 9 (6, 13) years. Partial correlations at baseline and 1 year between postprandial glucose excursions and glycated albumin/HbA_{1c}, after adjusting for fasting glucose, were 0.27/0.15 and 0.22/0.18, respectively. Glycated albumin, compared with HbA_{1c}, explained 66% more of the variation in postprandial glucose excursions at baseline. At 1 year, postprandial glucose excursions on basal, biphasic and prandial and insulin therapy were reduced by 0.43, 0.78 and 1.88 mmol/l, respectively. These reductions were associated with changes in both glycated albumin and HbA_{1c} ($P < 0.01$), with a stronger association for glycated albumin.

Conclusion Changes in glycated albumin and HbA_{1c} reflect changes in postprandial glucose excursions to a similar extent.

Introduction

Postprandial hyperglycaemia is an independent cardiovascular disease risk factor that may help explain the residual cardiovascular disease risk seen after adjustment for other classic risk factors [1–6]. Postprandial glucose levels, however, are difficult to measure in practice, with any differences in the post-meal measurement time introducing additional variation [3,4].

Glycated albumin, which reflects prevailing blood glucose concentrations over the preceding 2–4 weeks, has been proposed as an alternative marker for glycaemic control in patients with diabetes that preferentially reflects postprandial glycaemia [10–15]. Unlike HbA_{1c}, it is not affected by changes in erythrocyte survival time [16], nor by changes in albumin concentration [17], and is not subject to interference by endogenous glycated amino acids [17,18]. Glycated albumin may be useful as an alternative to HbA_{1c} to provide information on glycaemic control in the short term (2–4 weeks), and for monitoring glycaemic control in patients with haemoglobinopathies and iron deficiency (renal diseases), where HbA_{1c} measures are not considered to be robust [19–21]. Glycated albumin has also been evaluated as a useful marker for assessing the risk of atherosclerosis and microvascular conditions [14,22–24]. Recently, the usefulness of glycated albumin as a predictor of diabetic complications compared with HbA_{1c} was examined in two studies: the Atherosclerosis Risk in Communities (ARIC) Study and the Diabetes Control and Complications Trial (DCCT) [14,22–24]. Only a few studies have reported a high correlation between glycated albumin and HbA_{1c}, and their individual association with preprandial and postprandial glucose concentrations [10–12, 14,25,26]. Most of these studies were based on a small number of participants and the inferences regarding the correlation (degree of linear relationship) or association (regression) between glycated albumin or HbA_{1c} with fasting and postprandial glucose levels were drawn without considering the inherent dynamic relationship between pre- and postprandial glucose levels in people with established diabetes.

In the present study, we evaluated whether glycated albumin is more closely related to postprandial glycaemia than HbA_{1c}, and whether it better reflects the insulin-induced changes in postprandial glucose excursions seen in the Treating-to-Target-in-Type 2 Diabetes (4-T) trial [27,28].

Research design and methods

The design of the 4-T trial, and the follow-up results at 1 and 3 years, have been published [27,29]. Briefly, this was an open-label, randomized controlled, multicentre trial, which assigned 708 participants, who were receiving maximally tolerated doses of metformin and sulfonylurea but had suboptimum HbA_{1c} levels (7.0 to 10.0%), to the addition of twice-daily biphasic insulin aspart, thrice-daily prandial insulin aspart, or once-daily basal insulin detemir (twice if required). The primary outcome at 1 year was the HbA_{1c} level achieved, with a target of ≤ 48 mmol/mol (6.5%).

Biochemical analysis

HbA_{1c} levels, eight-point self-monitored capillary glucose (SMCG) profiles and fasting plasma samples for biomarker measurements were collected at baseline and at 1 year. Samples were surface-mailed overnight at ambient temperatures to the central laboratory. DCCT-aligned HbA_{1c} values (normal range 26–44 mmol/mol; 4.5–6.2%) were obtained by high performance liquid chromatography (Biorad Variant II; Biorad, Hemel Hempstead, UK). Glycated albumin levels were assayed enzymatically in duplicate at baseline and 1 year (Lucica GA-L kit; Asahi Kasei Pharma Corporation, Tokyo, Japan).

Statistical methods

Demographic and clinical characteristics were presented as number (%), mean $\pm$ SD or median (interquartile range), as appropriate. The reproducibility of the duplicate baseline and 1-year glycated albumin measurements were confirmed using Bland–Altman plots and coefficients of variation.

The arithmetic mean of duplicate glycated albumin measurements was used for all analyses. To avoid the influence of outliers in the distributions of fasting/postprandial glucose measures, HbA_{1c} and glycated albumin, and to account for possible non-linearity in the relationships, ‘robust correlation coefficients’ were calculated to explore the degree of (linear) relationships among them [30]. The possible non-linearity in the relationships among these variables are appropriately captured by this method, compared to the estimate of Kendall’s tau. Linear regression models were used to compare the changes in the levels of the measures of glycaemic control among the three insulin treatment regimens, and the robust standard errors were estimated with ‘study centre’ as clusters. At 1-year follow-up, 1.8% of HbA_{1c} data were missing and were imputed using the multiple imputation technique. No glycated albumin measurement was missing.

The exploration as to whether glycated albumin is more closely related to postprandial glycaemia than HbA_{1c} is not straightforward, given the complex dynamics inherent in the eight-point SMCG profile and the fact that glycated albumin and HbA_{1c} both reflect the overall glycaemic level. We used a statistically intuitive approach on a regression platform to address this issue: the associations of fasting SMCG/preprandial SMCG values, defined as the mean of the three preprandial and pre-bed values, with concomitant glycated albumin and HbA_{1c} values at baseline and 1 year were assessed using linear regression models, with adjustment for multiple treatments. The residuals from these regressions provided the glycated albumin or HbA_{1c} components which remained ‘unexplained’ by fasting/preprandial SMCG. These unexplained residual components were then regressed on the mean postprandial SMCG rise, defined as the mean of the three postprandial values minus the fasting/preprandial SMCG values. Given the approximate normality of the postprandial SMCG rise, simple regression models were fitted without adjustment for treatment effects and study centre effects. The formulation of this approach was as follows:

$$GA_{ij} = \mu + \text{fasting SMCG}'_{ij} \beta_1 = u_i + \varepsilon_{ij},$$

$$i(\text{patient}) = 1, 2, \dots, n; j(\text{centre}) = 1, 2, \dots, r$$

$$\text{ResidualGA} = \mu_i + \varepsilon_{ij} = UGA_{ij}$$

$$PPR_{ij} = \alpha + UGA'_{ij} \beta_2 + e_{ij}$$

where GA is glycated albumin, PPR is xxx and UGA is xxx.

The goodness-of-fit measures included adjusted R^2 , root mean squares of errors, and Bayesian information criterion. R^2 estimates provide the proportion of variation in the postprandial glucose excursion explained by ‘residual’ glycated albumin or ‘residual’ HbA_{1c}. A smaller estimate of the Bayesian information criterion would indicate stronger model fit in terms of information content, while compared between different regression models. Partial correlation coefficients were also used to explore the association of postprandial SMCG rise with glycated albumin and HbA_{1c}, having adjusted for fasting glucose levels.

Results

Of the 708 participants in the 4-T trial, 625 had the requisite data available for these analyses. The participants had a mean $\pm$ SD age of 62 ± 10 years, 65% were men, 92% were white, and their median (interquartile range) duration of diabetes was 9 (6, 13) years (Table 1). The distributions of anthropometric, clinical and biochemical study characteristics, including glycated albumin and HbA_{1c}, did not differ significantly at baseline among the three allocated insulin regimens. The glycated albumin assay was highly reproducible, with duplicate measurement coefficients of variation of 2.9% and 2.6% at baseline and at 1 year, respectively. The numbers of samples falling outside the 95% confidence lines of the Bland–Altman plot were 18 (3.04%) and 22 (3.52%), respectively, at baseline and 1 year.

At 1 year, participants in the 4-T trial achieved similar mean $\pm$ SD HbA_{1c} values on biphasic ($7.3 \pm 1.0\%$; 56 mmol/mol) and prandial [55 mmol/mol ($7.2 \pm 0.9\%$)] insulin, but values for participants on basal insulin were higher [6. mmol/mol ($7.6 \pm 1.0\%$); $P < 0.001$] for both comparisons). Similarly, the 1-year glycated albumin values achieved did not differ between the biphasic ($15.8 \pm 3.2\%$) and prandial ($15.4 \pm 3.9\%$) arms, and were higher in the basal arm ($16.7 \pm 3.4\%$; Table 2).

Robust correlation coefficients at baseline and at 1 year between HbA_{1c} and glycated albumin were 0.66 and 0.64, respectively ($P < 0.01$ in both cases). The relationships between glycated albumin and HbA_{1c} changes from baseline to 1 year in each treatment arm were linear, independent of insulin treatment effect, with only few outliers. The scatter plots between glycated albumin and HbA_{1c} with fitted Lowess regression lines are shown in Fig. 1A–C.

The correlations between fasting SMCG and HbA_{1c}/glycated albumin at baseline and 1 year were 0.55/0.53 and 0.29/0.28, respectively (Table 3); however, the degree of relationship of postprandial SMCG with glycated albumin was higher compared with that with HbA_{1c}: 0.62 vs 0.53 at baseline, 0.42 vs 0.35 at 1 year. The mean $\pm$ SD postprandial glucose excursions at baseline and 1 year were 2.67 ± 2.08 mmol/l and 1.77 ± 1.80 mmol/l, respectively. The partial correlation coefficients between glycated albumin and postprandial rise in glucose, controlling for fasting mean glucose, were marginally higher compared with those between HbA_{1c} and postprandial rise in glucose (0.27 vs 0.15 at baseline; 0.22 vs 0.18 at 1 year; Table 3). The patterns of association of fasting glucose, postprandial glucose and postprandial

glucose excursion with HbA_{1c} and glycated albumin, separately at baseline, are shown in Fig. 2A–F.

The changes in the levels of average SMCG, HbA_{1c} and glycated albumin were not independent of the treatment effects (Table 2). The fall in postprandial glucose excursion at 1 year was highest among participants treated with prandial insulin (1.88 mmol/l). From baseline to 1 year, postprandial glucose excursions fell by 29% with biphasic, 70% with prandial and 16% with basal insulin. Corresponding reductions in glycated albumin/HbA_{1c} of 24%/16%, 24%/16% and 17%/10%, respectively, were associated significantly (both $P<0.001$).

We further determined the patterns of associations of postprandial glucose rise with HbA_{1c} and glycated albumin at 1 year, separately according to insulin regimen, using a polynomial smoothing regression technique (Fig. 2C,F). Clearly, for each individual insulin regimen, the patterns of association were very similar, which confirms the similarity of these two biomarkers in relation to their association with postprandial glucose levels in people with Type 2 diabetes.

The effect sizes of ‘residual’ glycated albumin and HbA_{1c} (after eliminating the possible contribution of fasting glucose, and adjusting for treatment effects) on the postprandial glucose rise at baseline and 1 year are shown in Table 4. These regression coefficients are statistically significant, suggesting that both HbA_{1c} and glycated albumin can differentially explain postprandial rise in glucose level. Compared with the regression estimates associated with the variant of HbA_{1c} (residual HbA_{1c}), the higher estimates of standardized regression coefficients associated with residual glycated albumin (0.26 and 0.15 at baseline and year 1, respectively; Table 4) coupled with marginally smaller root mean square errors and Bayesian information criterion estimates suggest that glycated albumin could explain the postprandial rise in glucose level better only marginally compared with HbA_{1c}. Also, compared with HbA_{1c}, the correlation coefficients between postprandial excursions and residual glycated albumin were 44% higher at baseline (0.27 vs 0.15) and 18% at 1 year (0.22 vs 0.18).

Discussion

The 4-T trial evaluated the efficacy of randomized addition of a basal, prandial or premixed insulin regimen to dual oral therapy in people with Type 2 diabetes. The differential imposed changes in postprandial glucose rises provided an ideal opportunity to examine possible

differential relationships between HbA_{1c}/glycated albumin measurements and glucose measures. Glycated albumin appears to reflect current glycaemia as well as or marginally better than HbA_{1c}. Correlation coefficients between glycated albumin and postprandial glucose were higher both at baseline and 1 year (0.62 and 0.42), than those between HbA_{1c} and postprandial glucose (0.53 and 0.35). The partial correlation coefficient of postprandial glucose excursion with glycated albumin was marginally higher compared with that of HbA_{1c}, after adjusting for the effect of mean fasting glucose level.

Nathan *et al.* [14] reported a significant association of mean pre- and postprandial glucose concentrations with HbA_{1c} and glycated albumin, with a stronger association for glycated albumin (in terms of model R^2) in people with Type 1 diabetes. Their analyses were based on various additive multivariate modelling, but we did not report the standardized regression coefficients for comparisons with postprandial glucose excursion because the units of measurements for HbA_{1c} and glycated albumin were different. We adopted a different approach; our regressor was a variant of glycated albumin or HbA_{1c} measure, and postprandial excursion was the dependent variable. We have evaluated the association of postprandial glucose excursion with glycated albumin or HbA_{1c}, after eliminating the components of these glycaemic variables explained by fasting or preprandial glucose values. The present study shows that glycated albumin is associated with, but does not necessarily preferentially reflect, postprandial glucose. This suggests that glycated albumin could provide similar results to postprandial glucose and act as an alternative early indicator of diabetes and subsequent macro- and microvascular complications. It is worth mentioning that, while we explained the method for this evaluation in the simplest possible statistical way, the unexplained residual component was measured keeping in mind the effects of three insulin regimens in play.

Being the product of chemical condensation of haemoglobin and glucose, HbA_{1c} values are influenced by infection, haemoglobinopathies and renal failure [11,31]. Assessment of HbA_{1c} in people with these complications might lead to underestimation as a result of either shortening the life span of erythrocytes or altering of the proportions of young to old erythrocytes by erythropoietin [32]). There is some disagreement among researchers as to the degree that postprandial glucose, as measured by HbA_{1c}, relates to overall glycaemic

control; therefore, having a reliable concomitant marker, such as glycated albumin, could provide more accurate results.

The assay methods used to analyse the samples have been previously tested, with results showing no interference by endogenous glycated amino acids or changes in albumin concentration [33]; however, we also found that the glycated albumin assay gave reliable coefficients of variation. Glycated albumin is an index of the prevailing blood glucose concentrations over the preceding 2–4 weeks and gives a more accurate short-term result than HbA_{1c}; however, it does not capture long-term glycaemia measurements in the same way.

Although we found that glycated albumin and HbA_{1c}, measures of glycation, do not preferentially reflect postprandial glucose rises, we have confirmed a reliable short-term measure of glycaemic exposure. Closely correlated in all analyses with HbA_{1c}, glycated albumin showed a marginally stronger correlation with mean postprandial glucose and postprandial glucose excursion in a 24-h profile. The ability of the assay to quantitate glycoalbumin, an index of the prevailing blood glucose concentrations over the preceding 2–4 weeks, makes it a favourable candidate for use in the clinical setting to monitor glycaemic control in people with diabetes. Simultaneous measurement of glycated albumin and HbA_{1c} may be useful for the management of a postprandial hyperglycaemic state in people with diabetes and for the prevention of diabetic complications [34]. Other markers that may be more accurate in measuring glucose control include 1,5-anhydroglucitol [35] and fructosamine [34], but these require further investigation using data from large clinical trials.

Funding sources

The 4-T trial was sponsored and funded by Novartis Pharma AG, but conducted and analysed independently by the University of Oxford Diabetes Trials Unit. Glycated albumin assay kits were provided by Asahi Kasei Pharma Corporation.

Competing interests

S.K.P. has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator-initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi-Avensis and Pfizer. R.R.H. has received grants and personal fees from Merck Sharp & Dohme, grants

from Bayer, AstraZeneca, and personal fees from AMGEN, Bayer, Intarcia, Novartis, Novo Nordisk, and Owen Mumford Ltd., and other support from GlaxoSmithKline, Janssen and Takeda.

Acknowledgements

We thank Karen Fisher, Robin Carter and Rhiannon Klyne for technical support. The University of Melbourne gratefully acknowledges the support from the National Health and Medical Research Council and the Australian Government's National Collaborative Research Infrastructure Strategy (NCRIS) initiative through Therapeutic Innovation Australia.

References

1. Zenari L, Marangoni A. What are the preferred strategies for control of glycaemic variability in patients with type 2 diabetes mellitus? *Diabetes Obes Metab* 2013;**15** (Suppl. 2):17–25.
2. Aryangat AV, Gerich JE. Type 2 diabetes: postprandial hyperglycemia and increased cardiovascular risk. *Vasc Health Risk Manag* 2010;**6**:145–155.
3. Ceriello A. Point: Postprandial Glucose Levels Are a Clinically Important Treatment Target. *Diabetes Care* 2010;**33**:1905–1907.
4. Peter R, Okoseime OE, Rees A, Owens DR. Postprandial glucose - a potential therapeutic target to reduce cardiovascular mortality. *Curr Vasc Pharmacol* 2009;**7**(1):68–74.
5. Holman RR, Bethel MA, Chan JC, Chiasson JL, Doran Z, Ge J *et al.* Rationale for and design of the Acarbose Cardiovascular Evaluation (ACE) trial. *Am Heart J* 2014;**168**:23–29.e2.
6. McMurray RG, Bassin S, Jago R, Bruecker S, Moe EL, Murray T *et al.* Rationale, design and methods of the HEALTHY study physical education intervention component. *Int J Obes* 2009; **33**:S37–S43.
7. Standl E, Theodorakis MJ, Erbach M, Schnell O, Tuomilehto J. On the potential of acarbose to reduce cardiovascular disease. *Cardiovasc Diabetol* 2014;**13**:81.
8. McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA *et al.* Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362**:1477–1490.

9. McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA *et al.* Effect of valsartan on the incidence of diabetes and cardiovascular events (vol 362, pg 1477, 2010). *N Engl J Med* 2010;**362**:1748-.
10. Yoshiuchi K, Matsuhisa M, Katakami N, Nakatani Y, Sakamoto K, Matsuoka T *et al.* Glycated albumin is a better indicator for glucose excursion than glycated hemoglobin in type 1 and type 2 diabetes. *Endocr J* 2008; **55**:503–507.
11. Nagayama H, Inaba M, Okabe R, Emoto M, Ishimura E, Okazaki S *et al.* Glycated albumin as an improved indicator of glycemic control in hemodialysis patients with type 2 diabetes based on fasting plasma glucose and oral glucose tolerance test. *Biomed Pharmacother* 2009;**63**:236–240.
12. Koga M, Murai J, Morita S, Saito H, Kasayama S. Comparison of annual variability in HbA1c and glycated albumin in patients with type 1 vs. type 2 diabetes mellitus. *J Diabetes Complications* 2013; **27**: 211–213.
13. Huh JH, Kim KJ, Lee BW, Kim DW, Kang ES, Cha BS *et al.* The relationship between BMI and glycated albumin to glycated hemoglobin (GA/A1c) ratio according to glucose tolerance status. *PLoS One* 2014; **9**:e89478.
14. Nathan DM, McGee P, Steffes MW, Lachin JM. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. *Diabetes* 2014; **63**:282–290.
15. Wu WC, Ma WY, Wei JN, Yu TY, Lin MS, Shih SR *et al.* Serum glycated albumin to guide the diagnosis of diabetes mellitus. *PLoS One* 2016; **11**: e0146780.
16. Kosecki SM, Rodgers PT, Adams MB. Glycemic monitoring in diabetics with sickle cell plus beta-thalassemia hemoglobinopathy. *Ann Pharmacother* 2005; **39**:1557–1560.
17. Kouzuma T, Uemastu Y, Usami T, Imamura S. Study of glycated amino acid elimination reaction for an improved enzymatic glycated albumin measurement method. *Clin Chim Acta* 2004; **346**(2):135-43.
18. Paroni R, Ceriotti F, Galanello R, Battista Leoni G, Panico A, Scurati E *et al.* Performance characteristics and clinical utility of an enzymatic method for the measurement of glycated albumin in plasma. *Clin Biochem* 2007;**40**:1398–1405.
19. Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker. *Endocr J* 2010; **57**:751–762.
20. Zheng CM, Ma WY, Wu CC, Lu KC. Glycated albumin in diabetic patients with chronic kidney disease. *Clin Chim Acta* 2012; **413**:1555–1561.

21. Furusyo N, Hayashi J. Glycated albumin and diabetes mellitus. *Biochim Biophys Acta* 2013;**1830**:5509–5514.
22. Selvin E, Francis LMA, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL *et al.* Nontraditional Markers of Glycemia: Associations with microvascular conditions. *Diabetes Care* 2011; **34**: 960–967.
23. Furusyo N, Koga T, Ai M, Otokozawa S, Kohzuma T, Ikezaki H *et al.* Plasma glycated albumin level and atherosclerosis: results from the Kyushu and Okinawa Population Study (KOPS). *Int J Cardiol* 2013;**167**:2066–2072.
24. Song SO, Kim KJ, Lee BW, Kang ES, Cha BS, Lee HC. Serum glycated albumin predicts the progression of carotid arterial atherosclerosis. *Atherosclerosis* 2012; **225**:450–455.
25. Sakuma N, Omura M, Oda E, Saito T. Converse contributions of fasting and postprandial glucose to HbA1c and glycated albumin. *Diabetol Int* 2011;**2**:162–171.
26. Zhang T, He H, Yang HL, Huang HJ, Zhang MF, An ZM *et al.* [Study of glycated albumin cut-off point in diabetes mellitus and impaired glucose regulation]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2014;**45**:274–277, 298. [article in Chinese].
27. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S *et al.* Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007; **357**:1716–1730.
28. Holman R, Farmer A, Davies M, Levy J, Darbyshire J, Keenan J *et al.* Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes. *N Engl J Med* 2009; **361**:1736–1747.
29. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF *et al.* Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; **361**:1736–1747.
30. Niven EB, Deutsch CV. Calculating a robust correlation coefficient and quantifying its uncertainty. *Comput Geosci* 2012;**40**:1–9.
31. Yamada S, Inaba M, Okada S, Imanishi Y, Mori K, Emoto M *et al.* Association of glycated albumin, but not glycated hemoglobin, with calcaneus quantitative ultrasound in male hemodialysis patients with type 2 diabetes mellitus. *Metabolism* 2010; **59**:390–394.
32. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T *et al.* Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. *J Am Soc Nephrol* 2007;**18**:896–903.

33. Tahara Y, Shima K. Evaluation of error levels in hemoglobin A1c and glycated albumin in type 2 diabetic patients due to inter-individual variability. *Diabetes Res Clin Pract* 2010;**89**:115–120.
34. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M *et al.* Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol* 2014; **2**: 279–288.
35. Kim WJ, Park CY, Lee KB, Park SE, Rhee EJ, Lee WY *et al.* Serum 1,5-anhydroglucitol concentrations are a reliable index of glycemic control in type 2 diabetes with mild or moderate renal dysfunction. *Diabetes Care* 2012; **35**:281–286.

Fig. 1 Scatter plots with fitted Lowess regression lines showing relationship between (a) glycated albumin and HbA_{1c} at baseline, (b) glycated albumin and HbA_{1c} at 1 year, and (c) change in glycated albumin and HbA_{1c} at 1 year from baseline. Scatter plots are separately coloured for the three insulin treatment regimens.

Fig. 2 Scatter plots with fitted Lowess regression lines showing relationship between (a) mean fasting glucose and glycated albumin, (b) mean postprandial glucose and glycated albumin, (c) postprandial glucose excursion and glycated albumin, (d) mean fasting glucose and HbA_{1c} and (e) mean postprandial glucose and HbA_{1c}, and postprandial glucose excursion and HbA_{1c}, at baseline. Scatter plots are separately coloured for the three insulin treatment regimens.

Table 1 Baseline demographic and clinical characteristics of study participants (*N* = 625)

Demographic characteristic	
Men, <i>n</i> (%)	403 (64.5)
Mean (SD) age, years	61.7 (9.7)
Ethnicity, <i>n</i> (%)	
White	577 (92.3)
Mixed	7 (1.1)
Asian	29 (4.6)
Black	8 (1.3)
Other	4 (0.6)
Median (range) duration of diabetes, years	9 (6, 13)
Clinical and biochemical variables	
Mean (SD) BMI, kg/m ²	29.8 (4.6)
Mean (SD) waist measurement, cm	102 (12)
Mean (SD) systolic blood pressure, mmHg	138 (17)
Mean (SD) diastolic blood pressure, mmHg	79 (9)
Mean (SD) total cholesterol, mmol/l	4.1 (0.9)
Mean (SD) HDL cholesterol, mmol/l	1.03 (0.25)
Mean (SD) LDL cholesterol, mmol/l	2.4 (0.7)
Median (range) triglyceride level, mmol/l	1.6 (1.2, 2.2)
Glycaemic variables	
Mean (SD) HbA1c	
mmol/mol	71
%	8.6 (0.8)

Demographic characteristic	
Mean (SD) glycated albumin, %	20.11 (3.82)
Mean (SD) fasting SMCG, mmol/l	9.8 (2.5)
Mean (SD) postprandial SMCG, mmol/l	12.5 (3.0)

SMCG, self-monitored capillary glucose.

Table 2 Changes in glycaemic measures and postprandial glucose excursion at 1 year, stratified by insulin treatment regimen

Biomarker	Treatment	Marginal mean	95% CI	P value: vs biphasic	P value: vs prandial
Glycated albumin, %	Biphasic	-4.97	-5.59, -4.35	0.72	< 0.0001
	Prandial	-4.83	-5.43, -4.23		
	Basal	-3.25	-3.86, -2.64		
HbA _{1c} , %	Biphasic	-1.35	-1.50, -1.21	0.63	<0.001
	Prandial	-1.40	-1.59, -1.26		
	Basal	-0.83	-0.69, -0.69		
Fasting glucose, mmol/l	Biphasic	-2.96	-3.34, -2.58	0.24	0.031
	Prandial	-2.64	-3.02, -2.27		
	Basal	-2.06	-2.43, -1.70		
Postprandial glucose, mmol/l	Biphasic	-3.78	-4.28, -3.29	0.024	<0.001
	Prandial	-4.59	-5.08, -4.09		
	Basal	-2.56	-3.04, -2.09		
Postprandial glucose excursion, mmol/l	Biphasic	-0.78	-1.17, -0.39	<0.001	<0.001
	Prandial	-1.88	-2.27, -1.49		
	Basal	-0.43	-0.81, -0.06		

Table 3 Robust correlation between glycated albumin, HbA_{1c}, fasting glucose level and postprandial glucose level

	Baseline	1 year

	HbA _{1c} (%)	Glycated albumin (%)	HbA _{1c} (%)	Glycated albumin (%)
Fasting glucose (mmol/l)	0.55	0.53	0.29	0.28
Postprandial glucose (mmol/l)	0.53	0.62	0.35	0.42
Postprandial glucose excursion (mmol/l; partial correlation, adjusting for fasting glucose)	0.15	0.27	0.18	0.22

Table 4 Regression results to compare the ability glycated albumin and HbA_{1c} to explain postprandial rise in self-monitored capillary glucose levels

	Baseline standardized β	<i>P</i>	1-year standardized β	<i>P</i>
Residual glycated albumin	0.26	<0.01	0.15	0.008
Adjusted R^2	0.26		0.12	
Root mean square error	3.34		2.62	
Bayesian information criterion	3018.32		2522.46	
Residual HbA _{1c}	0.16	0.015	0.12	0.016
Adjusted R^2	0.10		0.10	
Root mean square error	3.37		2.63	
Bayesian information criterion	3027.93		2524.31

dme_13376_f1.tif

dme_13376_f2.tif

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Paul, SK;Holman, RR

Title:

Do glycoalbumin levels preferentially reflect changes in postprandial glucose excursions?

Date:

2017-09-01

Citation:

Paul, S. K. & Holman, R. R. (2017). Do glycoalbumin levels preferentially reflect changes in postprandial glucose excursions?. DIABETIC MEDICINE, 34 (9), pp.1284-1290. <https://doi.org/10.1111/dme.13376>.

Persistent Link:

<http://hdl.handle.net/11343/293024>