# Discordance Between $HbA_{1c}$ and Fructosamine

## Evidence for a glycosylation gap and its relation to diabetic nephropathy

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**OBJECTIVE** — Discordances between $HbA_{1c}$ and other measures of glycemic control are common in clinical practice and remain unexplained. We developed a measure of discordance between $HbA_{1c}$ and fructosamine (FA) (glycosylated serum proteins) to conduct a systematic evaluation. We termed this the glycosylation gap (GG) and sought to determine its relationship to diabetic nephropathy.

**RESEARCH DESIGN AND METHODS** — Measurements of $HbA_{1c}$ and FA on the same sample in 153 people were used to calculate GG, defined as the difference between measured $HbA_{1c}$ and $HbA_{1c}$ predicted from FA based on the population regression of $HbA_{1c}$ on FA.

**RESULTS** — GG had a broad distribution (range, −3.2% to 5.5%); 40% of samples had values indicating major differences in prediction of complications risk by the measured versus predicted $HbA_{1c}$. GG was highly correlated ($r = 0.81$) between measurements repeated in 65 patients 23 ± 2 weeks apart, indicating that the discordances are reliable and not explained by differences in turnover of underlying proteins. In 40 patients with type 1 diabetes of ≥15 years' duration, an increase in GG by 1% was associated with a 2.9-fold greater frequency of increasing nephropathy stage ($P = 0.0014$). GG was −0.8 ± 0.2% in subjects with no nephropathy, −0.3 ± 0.2% with microalbuminuria/hypertension, and 0.7 ± 0.3% in subjects with proteinuria or renal dysfunction ($P < 0.05$). GG correlated better with nephropathy than did either $HbA_{1c}$ or FA alone in this population.

**CONCLUSIONS** — The glycosylation gap may be a useful clinical research tool for evaluating physiologic sources of variation in diabetic complications beyond glycemic control.

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$HbA_{1c}$ is regarded as the gold standard for measurement of glycemic control and is invaluable in the treatment of diabetic patients. It is a predictor of diabetic complications, and interventions that reduce $HbA_{1c}$ correspondingly reduce the risk of complications (1–4). Whereas the overall utility of $HbA_{1c}$ is beyond question, discordances between $HbA_{1c}$ and other measures of glycemic control are commonly encountered (5–7) and are important because of the millions of yearly $HbA_{1c}$ measurements. Discordances between $HbA_{1c}$ and other clinically used biochemical measures of glycemic control have often been attributed to inadequacies or poor reliability of glucose self-testing and reporting or artifacts (5–8). Despite newer, more reliable technology, however, significant differences between measures of plasma glucose and glycemia estimated from $HbA_{1c}$ are still encountered. The 6- to 12-week time frame over which $HbA_{1c}$ equilibrates is an important consideration when comparing with shorter-term measures of plasma glucose, but temporal factors may not entirely account for persistent discordance (9–15).

The question arises whether discordances between $HbA_{1c}$ and other measures of glycemia are due to physiologic processes consistent within individuals over time. If this is the case, it is plausible that variation among diabetic patients in the intracellular glycation of proteins, independent of plasma glycemia, could affect the frequency of diabetic complications. We therefore wanted to test whether the discordance between $HbA_{1c}$ and a simple measure of integrated plasma glucose was reliable and bore a relationship to the frequency of a major complication, diabetic nephropathy. An important difference between plasma glucose and $HbA_{1c}$ is that the former reflects the physiology of glucose in the extracellular space, whereas $HbA_{1c}$ reflects nonenzymatic glycosylation (and depends on glucose concentration) in the intraerythrocyte compartment. We therefore selected fructosamine (FA) for comparison because it represents a clinically accessible measure of nonenzymatic glycation of proteins in the same compartment as plasma glucose, and should integrate plasma glucose fluctuations. The common perception is that FA results differ from $HbA_{1c}$ exclusively because of the difference in turnover times of the underlying glycation targets, hemoglobin versus serum proteins. The difference in physiologic compartments reflected in FA and $HbA_{1c}$ has not been the object of interest. It was therefore important to exclude the effect of the difference in turnover time by evaluating the reliability of discordances over a greater time than that in which the turnover of red cells or most serum proteins occurs. The study was conducted with prospective collec-

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**Abbreviations:** FA, fructosamine; GG, glycosylation gap.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tion of $HbA_{1c}$ and FA in the population, with assessment of diabetic nephropathy based on chart review.

## RESEARCH DESIGN AND METHODS

### $HbA_{1c}$-FA regression

**Patient population.** $HbA_{1c}$ and FA were both measured on the same sample from 153 people seen for diabetes drawn randomly from a university hospital–based diabetes clinic and private endocrine office practice. Exclusions included known hemoglobinopathies or erythrocyte disorders.

**Mathematical methods.** The glycosylation gap (GG) was calculated as the difference between measured $HbA_{1c}$ and $HbA_{1c}$ predicted from the FA based on the $HbA_{1c}$-FA regression equation

$$GG = \text{measured } HbA_{1c} - \text{predicted } HbA_{1c}$$

By this definition, GG is negative if measured $HbA_{1c}$ is less than $HbA_{1c}$ predicted from FA and positive if measured $HbA_{1c}$ is greater than predicted. GG is zero when $HbA_{1c}$ and FA are concordant. For example, $HbA_{1c}$ at the lower limit of normal and FA above the upper limit of normal would result in a negative GG, meaning the $HbA_{1c}$ is lower than predicted from the FA. If $HbA_{1c}$ is disproportionately higher than FA in patients with a complication of diabetes, increasing complications would be predicted as the gap becomes more positive, and conversely. No association would be expected if GG is random.

In subjects with repeated measurements of $HbA_{1c}$ and FA, the first and second pairs of values were used to examine variation in GG with time. If GG represented random variation in the $HbA_{1c}$-FA regression or resulted from differing time windows of exposure of serum albumin and the erythrocyte to glucose, consistency would not be expected.

Data were analyzed using JMP statistical software (SAS Institute, Cary, NC).

### Nephropathy staging

The analysis of nephropathy was performed in a subset population with type 1 diabetes of ≥15 years' duration according to the following criteria: Grade 0, normal renal function: urinary microalbumin ≤20 μg/min (24-h urine) or ≤17.9 μg/mg creatinine (spot urine); diastolic blood pressure <95 mmHg without antihypertensive therapy.

Grade 1, microalbuminuria or hypertension: urine microalbumin 20–200 μg/min (24 h) or 17.9–179 μg/mg creatinine (spot); or diastolic blood pressure >95 mmHg; or treatment for hypertension.

Grade 2, advanced renal dysfunction: >200 μg/min urinary microalbumin or >300 mg/24 h protein or serum creatinine >1.5 mg/dl.

Blood pressure was measured using a mercury sphygmomanometer with cuff size selected based on manufacturer's recommendation for arm diameter with the subject seated for 5 min.

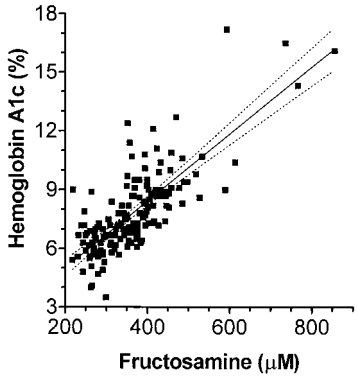


**Figure 1—***$HbA_{1c}$ and FA measured on the same sample in 153 patients. The regression line (solid) for the whole sample is $HbA_{1c} = 0.017 \times FA + 1.61$ (r = 0.78), with 95% confidence limits for the regression (dotted lines). Demographics: age, 47 ± 17 years; gender, 84 (55%) women and 69 (45%) men; race/ethnicity, 120 (78%) Caucasian, 28 (18%) African-American, 3 (2%) Asian-American, 2 (1%) unknown; diagnosis, 72 (47%) type 1 diabetes, 71 (46%) type 2 diabetes, 10 (7%) diabetes, type unknown.*

### Analytic methods

$HbA_{1c}$, FA, urinary albumin, protein, and/or creatinine, and serum creatinine were measured during routine clinical care without batching. $HbA_{1c}$ was measured in the laboratory of the Health Alliance of Greater Cincinnati using high-performance liquid chromatography (HPLC) ion exchange (Tosoh, Tokyo, Japan) (interassay coefficient of variation 2.9% at $HbA_{1c}$ 5.5%, 1.9% at $HbA_{1c}$ 10.0%). According to the manufacturer, carbamylated Hb does not interfere with the determination of $HbA_{1c}$ in this assay. Fructosamine was measured at Quest Diagnostics by autoanalyzer (Roche Diagnostics, Indianapolis, IN) with a nitroblue tetrazolium reaction, using a fructose-polylysine standard, interassay coefficient of variation 2%. Urinary microalbumin was measured by nephelometry, and urine protein was measured spectrophotometrically.

## RESULTS

### $HbA_{1c}$-FA regression

$HbA_{1c}$ and FA were highly correlated ($r^2$ = 0.61) (Fig. 1) in a population with widely varying glycemic control (see demographics in Fig. 1 legend): $HbA_{1c}$ (mean ±SD) was 7.9 ± 2.2%, FA 367 ± 98 μmol/l. The degree of correlation is very similar to previous reports (7–12,14,16). The regression line did not differ whether determined on the whole population or with exclusion of patients with type 1 diabetes of >15 years' duration, who form the basis for later analyses. Although there is a high degree of correlation, it is evident that there is substantial scatter as well. There was no difference in $HbA_{1c}$ and FA or the regression line between $HbA_{1c}$ and FA or GG by sex.

### Reliability and population variation of the glycosylation gap

To assess reproducibility of the glycosylation gap, we analyzed the relationship between consecutive determinations in 65 pairs of $HbA_{1c}$ and FA collected 23 ± 2 weeks apart (Fig. 2). There was a strong correlation ($r$ = 0.81) between the first and second determinations, with a $y$-intercept that did not differ from 0 and slope that was positive but not equal to 1. The paired measurements did not differ ($t$ test). Based on that, the sign of GG ap-

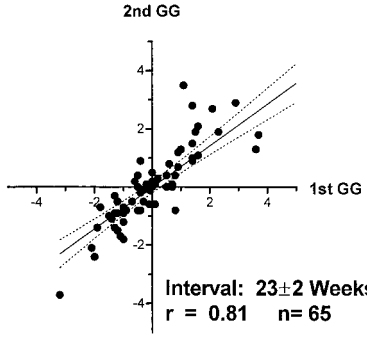


**Figure 2—***Relationship between paired glycosylation gaps determined within a subject on two separate occasions. Measurements were performed at follow-up visits with the indicated average interval.*

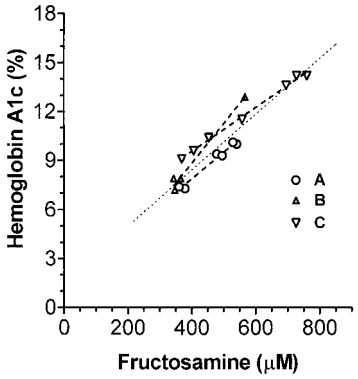


**Figure 3—***Regression lines for serial samples of paired $HbA_{1c}$ and FA in individual subjects A–C plotted in relationship to the regression line for the whole population from Fig. 1.*

pears highly reproducible, and the magnitudes of repeated determinations closely related. This is demonstrated over a time frame long enough to exclude effects of the physiologic differences in albumin versus erythrocyte turnover on GG.

To better assess intraindividual variability in the relationship of $HbA_{1c}$ to FA, the regression was plotted for individual subjects in whom multiple pairs of $HbA_{1c}$ and FA data over a time series were available (Fig. 3). The paired values could be highly correlated ($r \geq 0.98$ in each case shown) suggesting a fundamental physiologic relationship. The line of one subject (A) appears parallel to the population line, indicating that this individual's GG would be constant across the range of glycemic control. One example each is shown of subjects in whom the slope of the line is higher (B) or lower (C) than that for the population. These predict average GGs within subjects that are positive in both cases but rising in one case and falling in the other case as glycemic control deteriorates. This is a potential factor in the variability in magnitude of GG while the sign is more reproducible.

The distribution of GG was determined in the original population from which the measure was derived and in the subpopulation with type 1 diabetes of ≥15 years' duration. The distribution of GG in the original population was skewed toward positive values and not normally distributed (Shapiro-Wilk test), with median −0.20% and 25th and 75th percentiles of −0.8% and 0.7% (not shown). In the long-term type 1 diabetes population, the distribution of GG was normally distributed with mean ± SD −0.3% ± 1.0% (not shown). Twenty-seven (17%) and 36 (23%) patients had GG >1% below or above zero, respectively, indicating a large population in whom prediction of complications on the basis of measured $HbA_{1c}$ would differ substantially from that based on $HbA_{1c}$ predicted from FA and the $HbA_{1c}$-FA regression. An $HbA_{1c}$ decrement of 1–2% has reduced microvascular complications 40–70% (2–4).

### The glycosylation gap and nephropathy stage

Among subjects with type 1 diabetes of ≥15 years' duration, the glycosylation gap was −0.7 ± 0.2% with no nephropathy, −0.3 ± 0.2% with microalbuminuria/hypertension, and 0.7 ± 0.3% with proteinuria or severe renal dysfunction (Fig. 4) ($P = 0.005$ by ANOVA; $P < 0.05$ for a difference between stage 0 and stage 2 by post-hoc Student's *t* test). By ordinal logistic regression, there was a highly significant relationship found between GG and nephropathy: the relative frequency of advancing nephropathy stage, normalized per $HbA_{1c}$ unit, for GG was 2.9-fold (95% CI 1.4–6.1; $P = 0.003$); for $HbA_{1c}$, 1.3 (0.86–1.9; $P = 0.21$); and for FA 0.84 (0.59–1.2; $P = 0.31$). Of the 10 patients described as stage 2, a single patient was in chronic renal failure (not on dialysis) and one other patient had had a renal transplant. Relationships between nephropathy stage and either $HbA_{1c}$ or FA did not reach significance. After correction for the effects of urinary protein loss, the relative frequency of advancing nephropathy stage, normalized per $HbA_{1c}$ unit, for GG was 2.2-fold (95% CI 1.1–4.5; $P = 0.03$). Mean ± SE FA was 387 ± 11 μmol/l for all the subjects with type 1 diabetes of ≥15 years' duration, 394 ± 17 μmol/l in subjects with no nephropathy, 378 ± 21 μmol/l in those with microalbuminuria, and 386 ± 23 μmol/l in those with proteinuria, indicating no significant decline with worsening nephropathy ($P = 0.82$). $HbA_{1c}$ was 7.9 ± 0.2% in the entire subpopulation with diabetes of ≥15 years' duration, 7.6 ± 0.4% in subjects with no nephropathy, 7.7 ± 0.4% with microalbuminuria, and 8.7 ± 0.5% with proteinuria ($P = 0.15$). The regression between GG and nephropathy was not altered when $HbA_{1c}$, FA, or duration of diabetes were included as factors in the analysis. Results were similar when GG was expressed as a percentage of measured $HbA_{1c}$, which would normalize for $HbA_{1c}$ absolute magnitude. There was no effect of sex detected on multivariate ordinal logistic regression between glycosylation gap and nephropathy.

If the glycosylation gap were substantially altered by the presence of diabetic nephropathy, the population with long-term diabetes, which includes those with nephropathy, might be expected to have higher glycosylation gaps than those with short-duration type 1 diabetes. However, no difference was detected in the glycosylation gap between the subjects with type 1 diabetes of long versus short duration (−0.4 ± 0.2% vs. −0.5 ± 0.1%; $P = 0.63$, Wilcoxon test).

We sought to model the effects of glycated proteinuria on glycosylation gap. There is evidence that glycated albumin is no more likely to be lost in the urine than nonglycated albumin (17–19). At total body albumin daily synthesis of 13.9 g/person reported in patients with type 1 diabetes and nephropathy (20), GG would be altered by 0.1% for each 213 mg/24 h of urinary albumin at the group mean FA of 386. Albumin constitutes ~85% of the total urinary protein in diabetic nephropathy (21). When these factors were taken into account, the relative frequency of advancing nephropathy stage with GG remained significant, 2.2-fold per $HbA_{1c}$ unit (95% CI 1.1–4.5; $P = 0.03$).

## CONCLUSIONS

This study demonstrates that discordances commonly found among measures of glycemic control can be persistent and stable and related to a major complication of diabetes, nephropathy. The fact that the glycosylation gap, the $HbA_{1c}$-FA residual, correlates so well with a major complication of diabetes suggests shared factors between the origin of the discordance and the pathogenesis of the disease process. What does it mean that this study did not detect a relationship between $HbA_{1c}$ and nephropathy? The population was relatively small and the study may not have had the power to detect that effect.

The glycosylation gap could be affected by the production and disappearance rate of glycated hemoglobin, glycated serum proteins, or both. We are particularly interested in analyzing the variations found in otherwise healthy people with diabetes in whom urinary protein loss is not an issue, specifically

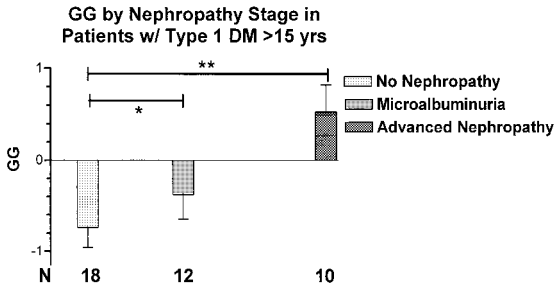


**Figure 4—***Mean GG in patients with type 1 diabetes of ≥15 years' duration as a function of nephropathy stage (as defined in* RESEARCH DESIGN AND METHODS*). Demographics: age, 44 ± 11 years; diabetes duration, 30 ± 10 years; gender 18 (45%) women and 22 (55%) men; race/ethnicity, 38 (95%) Caucasian, 2 (5%) African-American. For presence of a difference among the groups by ANOVA,* $P = 0.005$*. For differences between specific groups by post-hoc* t *test: * No significant difference; ** $P < 0.05$.*

whether it results predominantly from a gradient in protein nonenzymatic glycosylation between the two physiologic compartments. It is, however, possible that variations in the GG could be a consequence, rather than a marker or predictor, of nephropathy due to effects of proteinuria on protein turnover and FA. Patients with a high GG and high risk of nephropathy have a low FA in relationship to the $HbA_{1c}$. This would be the direction anticipated if albumin has a shorter survival time in the circulation, upon loss of glomerular selectivity (18,19). However, the lack of significant difference in FA by nephropathy stage is itself an argument that the findings are not explained by reduced FA in the group with urinary protein loss. Urine protein loss can contribute to the GG and can have a quantitatively important effect when present in the high microalbuminuric range. However, our modeling shows that a rise in glycosylation gap remained associated with increased nephropathy frequency even when such effects were taken into account. The observed effects are not solely a consequence of urinary protein loss. We were unable to detect a difference in GG by duration of type 1 diabetes expected if the gap is a consequence of nephropathy. Markedly positive GG values were found in patients with shorter durations of diabetes than those included in the complications analysis who do not currently have significant nephropathy, indicating that nephropathy is not necessary to have a positive GG. Other unrelated disease states that markedly perturb Hb or serum protein turnover could affect the GG, so these measurements must be assessed in clinical context.

These data demonstrate correlation between GG and nephropathy, not prediction. Hempe et al. (22) and McCarter et al. (23) have demonstrated that the hemoglobin glycosylation index, an analogous measure of discordance between self glucose–monitoring and $HbA_{1c}$, is also consistent and predicts both retinopathy and nephropathy, suggesting that the differences between extracellular and intracellular measures of glycemic control may precede nephropathy. Future prospective studies could delineate the cause-and-effect relationship in the regression of GG on nephropathy stage. The parallel between the Hempe et al. studies and ours that the discordances are between $HbA_{1c}$ and extra-erythrocyte measures of glycemic control strongly favors the concept that the discordances are systematic and potentially relevant to the pathophysiology of diabetic complications. It would also argue for an underlying mechanism that is related to the difference between the erythrocyte and plasma compartments. If, under carefully selected circumstances, the GG results predominantly from a gradient in protein nonenzymatic glycosylation between the plasma and intracellular compartments, it could represent previously unrecognized gradients in glucose concentration or factors that differentially alter the forward or reverse rates of nonenzymatic glycosylation. Variation in oxidation-reduction status (24,25) would be one important candidate. We have recently demonstrated population heterogeneity in the gradient established across the erythrocyte membrane by a radiolabeled nonmetabolizable glucose analog, 3-*O*-methylglucose, incubated with glucose-depleted erythrocytes (26). This supports the concept of variability in the red cell membrane glucose gradient. The data do not distinguish among these or other candidate mechanisms.

Several caveats: The population used for the complications analysis was a subgroup of the population in which GG was defined rather than an independent population. However, the regression generated with a subpopulation that did not overlap with that for the complications analysis was identical. The nephropathy end points were based on American Diabetes Association standard of care Clinical Laboratory Improvement Amendments–certified routine clinical monitoring of patients, not research assays. Carbamylated hemoglobin can accumulate in erythrocytes of uremic patients (27–31), and it is important to ensure that carbamylated Hb is not a confounder. Whereas the manufacturer indicates that carbamylated Hb does not affect the method used here, there is limited evidence challenging this assertion (32). The urea nitrogen concentration was closely clustered in 38 of our 40 nephropathy analysis subjects, making a carbamylated Hb effect on these results unlikely (not shown). Most of the patients were at stable glycemic control when sampled, and Fig. 3 indicates that the $HbA_{1c}$-FA relationship can be extremely stable within subjects. If samples are collected early after changes in glycemic control, that could reduce the GG stability over time.

Shortened red cell survival associated with renal failure would have an effect opposite to the relationship found, making it unlikely to be a contributor to our findings.

In summary, we observed consistent discordances between $HbA_{1c}$ and an extra-erythrocyte measure of glycemic control, FA. Changes in glycosylated proteins resulting from nephropathy do not appear to explain these findings but have not been ruled out conclusively. When this discordance is quantitated in the form of a glycosylation gap, it correlates with the frequency of a major microvascular complication of diabetes. We propose that the glycosylation gap will be useful as a research probe quantitating variation between the two underlying tests of glycemic control to identify sources of population variation in diabetic complications beyond glycemic control per se. Prospective studies will be necessary to determine whether repeated determinations should

alter decision-making regarding risk for future complications in the individual patient.

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