The Glycation Gap and Estimated Glomerular Filtration Rate in Individuals without Diabetes Mellitus

To the Editor:

The glycation gap (GG), the difference between measured glycosylated hemoglobin (Hb A1c) and Hb A1c predicted from fructosamine, has been used to quantify nonglycemic differences in formation of Hb A1c between individuals, but the technique is controversial. An increased GG in patients with diabetes has been associated with nephropathy diagnosed primarily by proteinuria. The GG can be calculated irrespective of glycemia, that is, in normoglycemic as well as hyperglycemic individuals. We therefore hypothesized that, in individuals without diabetes, chronic kidney disease (CKD) would be associated with an increased GG compared with those without CKD.

We studied a nonprobability convenience sample, after applying exclusion criteria, of 949 patients in the community whose CKD stage was based on estimated glomerular filtration rate (eGFR) (5). Over a 4-month period, we analyzed samples from primary care mostly on receipt and all within 24 h. Exclusion criteria were diabetes mellitus, pregnancy, age <16 years, hemoglobinopathy, unknown ethnicity or not of white or South Asian ethnicity, hemoglobin ≤9.0 g/dL, and albumin <3.0 or >5.0 g/dL.

Laboratory analyses were performed by routine methodology in an accredited laboratory with acceptable and stable performance throughout the study period. Hemoglobin (flow cytometry, Sysmex XN-10®, Sysmex Corp.), Hb A1c (ion-exchange HPLC, National Glycohemoglobin Standardization Program certified, G7 HPLC analyzer, Tosoh Corp.), fasting glucose (hexokinase), creatinine (compensated kinetic Jaffe with rate blanking), albumin (bromocresol green), and fructosamine (nitro-tetrazolium blue) were measured (Modular® P analyzer, Roche Diagnostics). CKD stages <3, 3, 4, and 5 were based on eGFR levels of ≥60, 30–59, 15–29, and <15 mL·min⁻¹·(1.73 m²)⁻¹, respectively. All patients were in CKD stage ≥3 except for 2 (0.2%) with CKD 4. Because of the small numbers of those in CKD stage >3, the 2 patients were removed, with further analysis examining only those in stage 3 and below. Permission for data to be published has been granted by the Royal Wolverhampton NHS Trust Caldicott Guardian.

We calculated the GG by converting fructosamine into a standardized normal deviate by subtracting the mean fructosamine from each value and dividing the result by the SD of fructosamine. This value was then converted into an estimate of Hb A1c by multiplying it by the SD of Hb A1c and adding the mean Hb A1c. From the measured Hb A1c for each sample, we subtracted its respective estimated Hb A1c to calculate the GG, and the GG was compared between those with CKD stage 3 and those with CKD stage <3. We then tested for the association between GG and presence of CKD stage 3 (yes/no) using multivariable forced logistic regression modeling with the presence of CKD 3 (yes/no) as the outcome measure (Table 1, model 1). Independent variables known to affect the GG were controlled for in this model including age, sex, ethnicity (white or South Asian), hemoglobin, fasting glucose, and fructosamine (Table 1, model 1). To address concerns with regard to GG calculation and interpretation, a second model (Table 1, model 2) was run with GG excluded and Hb A1c included to test the influence of Hb A1c on CKD with the influence of fructosamine and glucose statistically removed. Multicollinearity diagnostics of variance inflation factors confirmed reasonable independence before analysis.

Of 947 patients, 793 (83.7%) had CKD stage <3 (58% female) and 154 (16.3%) had CKD stage 3 (55% female) (Table 1). Those with CKD stage 3, compared to those with CKD stage <3, were older, but despite higher glycemic markers, their GG was similar. When controlled for independent variables and compared to CKD stage <3, the GG was not associated with CKD (model 1), and neither was Hb A1c (model 2). The only variable that significantly predicted CKD stage was age. These data suggest that the GG is not associated with CKD in nondiabetic individuals, defined according to eGFR.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Acknowledgments: The authors thank the laboratory staff of New Cross Hospital for their assistance with sample analysis.

References

Combining Serum Carbohydrate-Deficient Transferrin and Hair Ethyl Glucuronide to Provide Optimal Information on Alcohol Use

To the Editor:

Weykamp et al. recently reported on their efforts toward the harmonization of carbohydrate-deficient transferrin (CDT) measurements in serum (1). Alcohol biomarkers play a key role in the identification of alcohol abuse, a chronic disorder with enormous health and legal implications. CDT is a widely used biomarker for the detection of excessive alcohol use that has a high diagnostic sensitivity and specificity and cannot be compared to traditional biomarkers such as alanine and aspartate aminotransferase, γ-glutamyl transferase, and blood count indices (2). However, CDT’s diagnostic ability depends on many factors including sex, age, metabolic diseases, and mutant transferrins (3). Although used widely in clinical practice, CDT has a half-life of about 10 days and, therefore, estimates the excessive use of alcohol only over the past month rather than the length of the disorder. When such extensive efforts are directed to harmonize measurements for CDT throughout labora-

Table 1. Differences between patients with CKD stage <3 and 3 and correlates of CKD 3 in 2 different regression models.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CKD stage &lt;3</th>
<th>CKD stage 3</th>
<th>Regression model 1: Presence of CKD stage 3</th>
<th>Regression model 2: Presence of CKD stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>793</td>
<td>154</td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Male</td>
<td>333 (82.8)</td>
<td>69 (17.2)</td>
<td>0.418</td>
<td>0.493</td>
</tr>
<tr>
<td>Female</td>
<td>460 (84.4)</td>
<td>85 (15.6)</td>
<td>0.418</td>
<td>0.493</td>
</tr>
<tr>
<td>White</td>
<td>575 (81.0)</td>
<td>135 (19.0)</td>
<td>&lt;0.001</td>
<td>0.119</td>
</tr>
<tr>
<td>South Asian</td>
<td>218 (92.0)</td>
<td>19 (8.0)</td>
<td>0.63 (0.36–1.12)</td>
<td>0.119</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.8 (17.1)</td>
<td>71.7 (13.9)</td>
<td>0.108 (1.06–1.09)</td>
<td>0.108 (1.06–1.10)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.2 (1.5)</td>
<td>13.9 (1.4)</td>
<td>0.94 (0.80–1.11)</td>
<td>0.94 (0.80–1.11)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.2 (0.9)</td>
<td>5.4 (0.8)</td>
<td>1.03 (0.81–1.32)</td>
<td>0.796</td>
</tr>
<tr>
<td>Fructosamine (mmol/L)</td>
<td>225.8 (23.3)</td>
<td>233.7 (22.4)</td>
<td>&lt;0.001</td>
<td>0.460</td>
</tr>
<tr>
<td>Hb A\textsubscript{1c} (mmol/mol)</td>
<td>39.8 (6.5)</td>
<td>41.6 (5.8)</td>
<td>&lt;0.01</td>
<td>0.98 (0.94–1.01)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.54 (0.3)</td>
<td>4.42 (0.3)</td>
<td>&lt;0.001</td>
<td>0.99 (0.91–1.08)</td>
</tr>
<tr>
<td>Glycation gap (mmol/mol)</td>
<td>0.13 (6.9)</td>
<td>0.01 (6.8)</td>
<td>0.848</td>
<td>0.264</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Data are n (%) or mean (SD) unless noted otherwise.


Letters to the Editor

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Previously published online at DOI: 10.1373/clinchem.2014.223545

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Clinical Chemistry 60:10 (2014) 1347