

Toward a Better Understanding of Diabetes Risk

It is the contention of the author that individuals do not take diabetes seriously enough and that recognition and understanding could be improved by conversion of the surrogate biomarker, A1c to blood sugar in mg/dl.

The Problem

Is concern or lack of it by the general public to the risks and complications of diabetes. By diabetes the author refers to type 2 which was once restricted to adult populations but is now found in adolescents and children and has increased in these younger populations by 30% between 2001 and 2009 (1). Results of a survey taken by AARP in spring 2019 asking seniors to list what they most fear about the future showed Alzheimer's on 24% of the responses, cancer on 21% but diabetes appeared on only 4% of responses (2). Even in patients with confirmed diagnosis of diabetes, only one fourth achieved diabetes care targets (3).

Reasons for greater concern

There has been considerable progress in reducing cancer incidence in the United States. The number of cancer survivors continues to increase due to the aging and growth of the population and improvements in survival rates (4) while the number of people with diagnosed and undiagnosed diabetes will increase from 23.7 million to 44.1 million in 2029 with ~65% of individuals of this population being overweight or obese (5). In Puerto Rico, which has among the highest incidences of diabetes in the nation at 16%, it is shown, using data from the department of health, (6) that confirmed diabetics are 25 times the number of registered cancer patients and 39 times the number of persons with Alzheimer's. Finally, if not already enough, diabetes predisposes individuals to circulatory problems. In persons with type 2 diabetes, the risk of having an incident myocardial infarction or stroke is increased 2- to 3-fold and the risk of death is increased 2-fold, independent of other known risk factors for cardiovascular diseases (7).

Possible reasons for less concern

Imagine yourself as a patient upon being notified that a tumor has been spotted in your lung or amyloid plaque has accumulated in your brain. Would this diagnosis elicit the same visceral response as "the proxy for your blood sugar is a little high." Highly unlikely. Tumors and plaque are alien to the body, things to be fearful of. Blood sugar or glucose is a natural substance that helps sustain life, something we need.

The problem is the **excess amount**. In a chemical process that occurs in all of us, glucose attaches in a non-enzymatic reaction, called glycation, which involves condensation of aldehydes, ketones, and reducing sugars with amino groups on proteins, peptides, and amino acids to form glycated proteins including hemoglobin. Since hemoglobin has a lifespan of 100-120 days it will reflect the **average** glycation which is consistent over this time span. This measurement is superior to a randomly collected sample in which glucose can vary widely depending upon dietary, emotional and other factors. Over time, glycemic reactions can further lead to formation of advanced glycation end products (AGEs), which can cause the development of diabetic complications and various diseases associated with aging (8). Furthermore, tissue accumulation of AGEs is not uniform in different organs. AGE tissue specificity has been demonstrated in kidney, retina, and brain (9) with implications for the eventual conditions of blindness, end-stage kidney disease, painful neuropathy, amputation, stroke, and mortality. These outcomes are slow to appear and hardly associated with "the proxy for your blood sugar is a little high." So what might be done to help individuals better understand the consequences of excess blood sugar?

A possible solution

Make the proxy more meaningful. This refers to the surrogate which is glycated hemoglobin A1c, shortened to HbA1c and more recently to A1c, just letters and a number which disconnects with any physiological meaning. What exactly **IS A1c**? The answer is a peak on a chromatographic column (see the figure)(10) (note –it is the third peak, following A1a and A1b).

Also shown in the figure is that the concentration of glucose is proportional to the percent A1c. The discovery of this

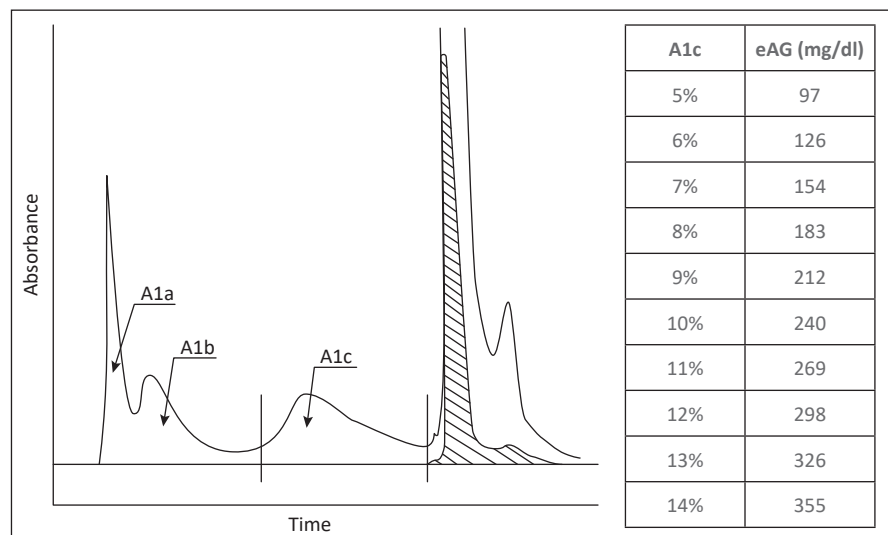


Figure 1. Chromatography of Gly HbA1c (left) Correlation to Blood glucose (right).

relationship has been described by Rahbar (8), who isolated a minor “abnormal fast-moving hemoglobin band” in diabetic patients during routine screening for hemoglobin variants. This finding later turned out to be an important marker with clinical and pathological applications. Measurement of HbA1c in diabetic patients is now an established procedure for evaluating long-term control of diabetes. This is not to say that exclusive use of A1c does not have its critics. In a recent viewpoint article it has been argued that other measures of the quality of diabetes care may better represent the outcomes that are truly meaningful to people living with diabetes, including immediate symptoms of hypoglycemia or hyperglycemia, burden of treatment and quality of life (11).

The suggestion

To make this surrogate more understandable by converting it back to units of glucose in mg/dl using the information in the figure. So instead of A1c =8.0, we would have Glucose= 183mg/dl (A1c results are given to one decimal place so the value of glucose can easily be extrapolated). All that would need to be done is to program the monitoring device to make this conversion. The general public would then be able to evaluate their diabetic or non-diabetic status in units they understand. Whether the statement of “your blood sugar is a little high” will have any greater effect on concern about diabetes than “your proxy for blood sugar is a little high” remains to be seen.

Alan M. Preston, PhD. Biochemistry Department, University of Puerto Rico, Medical Sciences Campus. Email: alan.preston@upr.edu

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