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The Why and Wherefore of Fructosamine

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Before measures of glycosylated hemoglobin (GH) were available, clinicians and researchers evaluating diabetic patients could only infer overall blood glucose control. Clinicians attempted to extrapolate glycemic control from occasional fasting or random blood glucose measurements, while researchers used indirect (and often inaccurate) parameters of control such as number of insulin injections per day. The introduction of the GH measurements in the mid 1970s made possible accurate assessment of overall glycemia for a defined time period. Clinicians could assess the efficacy of therapeutic interventions, and investigators could accurately evaluate the influence of blood glucose control on any number of outcomes. In 1982, another measure of glycemic control, fructosamine (FA), was made available. Herein, we examine the clinical utility and interpretation of the GH and FA measurements.

Overview

Both GH and FA are measurements of the degree to which plasma proteins undergo irreversible, nonenzymatic glycosylation (Figure). Glycosylation proceeds at a rate proportional to the serum glucose at any time (1). Therefore, the higher the blood glucose throughout the life span of the protein, the more protein becomes glycosylated. In this way, the average blood glucose for a specific period of time, dictated by the life span of the protein, can be estimated.

The clinician can compare the glycosylated protein measurement with that obtained before or after clinical interventions, such as institution of oral hypoglycemic therapy or intensification of an insulin program. These measurements can also be used to provide feedback to the patients about their metabolic control and perhaps to develop a "goal" level of control.

In research studies, such as the Diabetes Control and Complications Trial, the glycosylated protein result can be used to stratify patients into groups with various levels of control.

Unfortunately, a specific average blood glucose value cannot be attributed to a specific value for a glycosylated protein, so only broad estimations of average blood glucose are possible (2). Therefore, GH and FA results should not be used as tests for the diagnosis of diabetes mellitus or other syndromes of glucose intolerance (3,4).

That these measurements are truly average readings is another limitation. The same GH or FA value may result for a patient whose measured blood glucose levels are consistently 200 mg/dL as for a patient whose measured blood glucose levels are 100 mg/dL half the time and 300 mg/dL the other half of the time. Oversimplified, this illustration does emphasize that measurement of GH or FA does not replace the office measurement of blood glucose or self-monitoring of capillary blood glucose by the patient. Only through actual measurements of blood glucose can hypoglycemia or hour-to-hour variation in blood glucose be detected and specific changes in insulin regimens be rationally prescribed.

In summary, measurements of GH or FA are most useful for evaluating intermediate-term blood glucose control and assessing the efficacy of therapeutic interventions that may affect control. They can also be used to compare the degree of overall glycemia in large groups of patients. They are an adjunct to, not a replacement for, traditional diagnostic and monitoring techniques.

Glycosylated Hemoglobin

GH was the first glycosylated protein measurement clinically available and is therefore the most extensively studied and employed measure of metabolic control. A number of different hemoglobin A subfractions are measurable, but the hemoglobin A_{1C} component is the most widely reported because it comprises the majority of glycosylated hemoglobin and is least affected by recent fluctuations in blood glucose (5). It assesses the overall blood glucose over a four- to eight-week period (6).

Values are reported as a percentage of the total hemoglobin which is glycosylated. Normal ranges for GH differ in different

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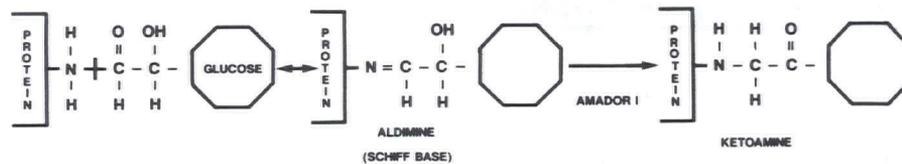
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Figure—Display of the reversible nonenzymatic glycosylation of proteins to the aldimine form. These compounds spontaneously undergo an irreversible Amadori rearrangement to the more stable ketoamine compound. With the GH measurement, the protein involved is hemoglobin; with FA, it is a variety of serum proteins.

Table
Correlation of GH and FA in Diabetic Patients*

Study	Number of Patients	Correlation Coefficient
Allgrove & Cockrill (7)	61 diabetic 30 control	r = 0.69
Baker et al (9)	42 diabetic 30 control	r = 0.82
Dominiczak et al (12)	77 diabetic	r = 0.20
Negoro et al (10)	53 diabetic 93 control	r = 0.73
Smart et al (11)	204 diabetic	r = 0.80
Sobel & Abbassi (2)	33 diabetic	r = 0.59
Henry Ford Hospital†	100 diabetic	r = 0.69

*Results of six studies in which the correlation of GH and FA in diabetic patients is reported. The r value was statistically significant ($P < 0.05$) in all but the Dominiczak study.

†Unpublished data from Henry Ford Hospital show a good correlation between the two measurements.

GH = glycosylated hemoglobin, FA = fructosamine.

laboratories and with different assay techniques. In comparing results with different normal ranges, it is best to compare the number of standard deviations from the mean of each value, rather than the absolute result. (In the assay being used at present at Henry Ford Hospital, a high-performance liquid chromatography method employing ion-exchange columns, the mean is 4.9% for nondiabetic control subjects and the standard deviation is 0.4%. So, the mean \pm 2 standard deviations results in a "classic" normal range of 4.1% to 5.7%. A value of 8.1%, for example, would be 8 standard deviations above the mean value for nondiabetics.) The use of GH as a measure of overall glycemia is limited because it is a difficult test to perform with precision and accuracy (7), is expensive, and can be misleading in patients with hemoglobinopathies or hemolytic anemias (5). In clinical practice, these represent rare but significant problems.

Fructosamine

The fructosamine assay measures a variety of serum proteins which, like hemoglobin, after glycosylation form ketoamines by the Amadori reaction (Figure). They are termed fructosamines because the sugar component of the compound is converted from glucose to fructose during formation of the ketoamine. These substances can serve as reducing agents in alkaline solu-

tion allowing for easy, rapid, and inexpensive laboratory measurement (8).

As shown in the Table, in most trials FA and GH measurements correlate well, with correlation coefficient (r values) between 0.59 and 0.82 (2,7,9-11). In our experience at Henry Ford Hospital, we have also found a good correlation between GH and FA. In August 1988, we obtained simultaneous FA values in 100 consecutive diabetic subjects in whom a GH was obtained. Among these subjects, the r value for the correlation of GH and FA results was 0.69.

One study failed to note a significant correlation between the two measurements in a diabetic population, with an r value of 0.20 (12). It is not clear why the two measurements did not correlate in this study, although it is possible that these represent patients in whom metabolic control is fluctuating rapidly.

In contrast to GH, FA reflects overall blood glucose control over the previous one to two weeks (2). This relatively short time frame is a major clinical limitation to the use of FA as an estimate of overall glycemia. Recent marked changes in glyce-mic control can provide a false impression of longer term control.

A less common problem with the FA assay is characterized by situations of increased protein loss or turnover that may cause an inaccurately low value (7).

A Comparison of GH and FA

GH is the more widely used, studied, and accepted marker of glycemic control in diabetic patients. We feel that this experience grants the GH test an insurmountable advantage over FA, despite the former being more difficult and expensive to perform. Present standards of medical care for patients with diabetes, as promulgated by the American Diabetes Association (13), state that a "GH be performed at least semiannually in all diabetic patients and preferably quarterly in insulin-treated diabetic patients and in non-insulin-treated patients with poor metabolic control." Since GH assesses blood glucose control over a one- to two-month time frame, obtaining a GH value more often than quarterly is inappropriate in most clinical situations. The FA assay should be reserved for specific scenarios, as in the patient with a hemoglobinopathy or when short-term changes in glyce-mic control are required, as in the pregnant diabetic patient. In most other situations, the GH is the preferred marker.

Summary

GH and FA are useful monitors in the care of diabetic patients. For most situations, GH is the preferred test and should be routinely monitored. FA should be reserved for exceptional situations in which blood glucose control over one to two weeks must be assessed or in patients with a hemoglobinopathy. Patients with diabetes should be advised of their present GH level and the preferred goal.

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