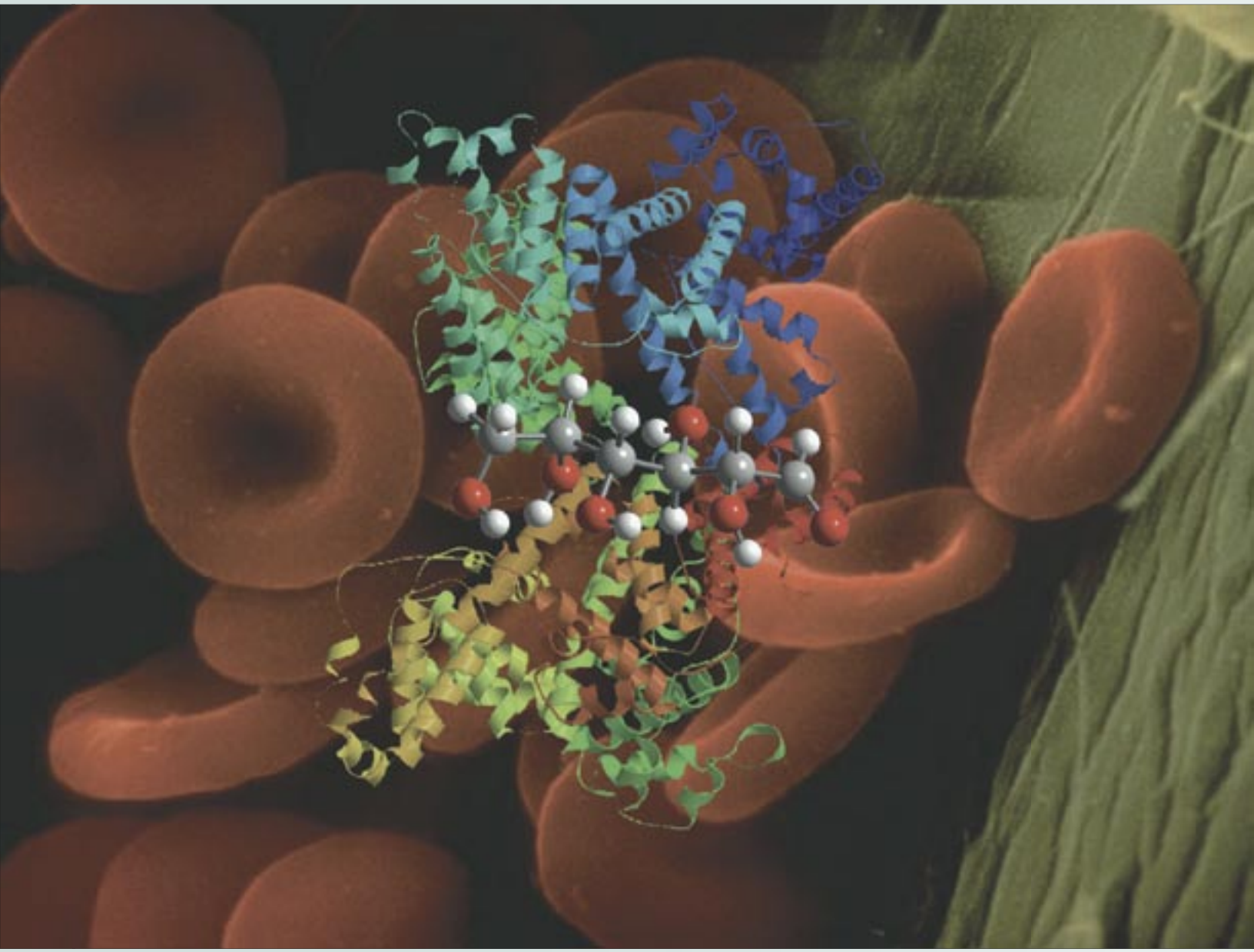

Towards A New Glycation Index

EPINEX DIAGNOSTICS INC.

Corporate Monograph Series - 1

Foreword

This monograph, prepared by our esteemed scientific advisor, Dr. Vern Roohk, presents a detailed introduction to the biological principles that underlie our G1A® Rapid Diabetes Monitoring Index Test for glycated albumin, developed by Company co-founder, Dr. Henry Smith. I hope that this presentation will encourage an ongoing scientific dialogue among specialists in the field of diabetes research and management that can only improve the available options for patient diagnosis and treatment.

This is the first in a series of corporate monographs that will highlight the research and development activites of our company. I would like to acknowledge the efforts of the following contributors: Dr. Vern Roohk, Scientific Advisor; Dr. Ping Wang, Research Advisor; Dr. Henry Smith, Chief Technical Officer; Dr. David Trasoff, Corporate Communications; and Ms. Azra Zaidi, Director of Research and Development.

Asad R. Zaidi, President
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About Epinex

Epinex Diagnostics, Inc., a privately held California corporation, is developing rapid assays, or tests, for point-of-care and over-the-counter use. These tests have the potential to make critical medical information quickly, easily and affordably available to doctors, health workers, and to the average person at home. The medical and economic implications for these tests promise a revolution in health care. Epinex Diagnostics was founded in 2002 by three pioneers in the biomedical device industry, with a combined experience of more than 70 years in biochemical engineering, product design and development, and medical device marketing. They have been joined by an advisory board of distinguished scientists, experts in marketing and management, and leaders in the field of diabetic care, including Dr. Ping Wang, Director of the world-renowned Joslin Diabetes Center at the University of California, Irvine.

Epinex is preparing to launch the G1A® Rapid Diabetes Monitoring Index Test, a patent-pending rapid test for monitoring diabetes that utilizes disposable test strips and a matched instrument for reading the result. This test promises to revolutionize diabetes care by providing a better way for diabetics and their physicians to monitor and manage excess glucose in the blood, and thereby improve control over the long-term complications associated with the disease. The patent for the G1A® Rapid Diabetes Monitoring Index Test was recently published by the WTO and the European Patent Commission.

Currently-available test procedures leave a gap in effectively monitoring a diabetic's long-term health, which the Epinex G1A® Index is designed to fill. The test has tremendous potential to improve patient care and effect savings to the healthcare system and to society as a whole; and to become the diagnostic standard for diabetes. With diabetes looming as an epidemic throughout the world, there is a clear need for a more effective test than those currently available.

Towards a New Glycation Index

Vernon H. Roohk, Ph.D.

Introduction

The diagnosis and clinical assessment of diabetes mellitus, a rapidly escalating healthcare problem throughout the world, has gradually transformed from the simple measurement of excessive blood sugar to an ongoing assessment of the metabolic consequences of that excess. This transformation has been driven by an understanding, gleaned from basic and clinical research, of the linkage between metabolic products and the long-term damage they cause. The measurement of glycated protein in the blood has emerged as the most significant marker for long-term disease management. In this regard the measurement of glycated hemoglobin, specifically hemoglobin (Hb) A1c, has become a gold standard for physicians and clinicians worldwide. Other glycated serum proteins are also of distinct interest since they represent a shorter residence time in the blood and therefore reflect briefer, more recent histories of hyperglycemia. Because albumin constitutes the major component of serum protein, glycated albumin is of particular significance as a marker of short term glycemia.

The current literature may be broken down into glycemic indicators that provide long-term information, intermediate-term information, and short-term information regarding the diabetic patient. The utility of hemoglobin A1c as a measure of glycated hemoglobin in blood as a function of blood sugar level has been thoroughly reviewed in Diabetes Care (2003). Since most hemoglobin resides in the red blood cell and red blood cells live about 120 days, the relative amount of glycated hemoglobin in a patient's blood becomes a living record of hyperglycemia over a period of a few months. The measurement of A1c concentration when compared to that of total hemoglobin provides the physician with long-term information, which becomes gradually updated with the next generation of erythrocytes. The A1c test has become a gold standard because it has been shown to reliably predict the risk for the development of diabetic complications.

Short-term indicators usually refer to, but are no longer limited to, measurements of blood glucose concentration as measured either in blood, plasma, or serum. Present-day technology allows a diabetic to monitor his or her own blood glucose level at home by capillary stick and automated glucose monitor, thus the term self-monitored blood glucose (SMBG) for this measurement method. Glycemic control today is best judged by the results of both A1c and SMBG. Correlation between mean plasma glucose and A1c is linear and tables are widely published. The substitution of fasting plasma glucose (FPG) tends to progressively underestimate the A1c value; thus FPG alone should be used with caution as a predictor of long-term glycemia. The American Diabetes Association (ADA) currently recommends a target A1c of less than 7%. However, there are many patients who meet diagnostic criteria for diabetes by the oral glucose tolerance test (OGTT), the clinical standard, but not by FPG, who have an A1c of less than 7%. For this reason the A1c is not recommended at this time for diagnosis of diabetes.

The A1c test is nevertheless an important indicator of glycemic control, and it is recommended at least twice a year for patients whose control is stable and quarterly for patients whose therapy has changed or who are not meeting glycemic goals. The A1c test is not known to show changes in glycemic control in less than 2-3 months. Several studies suggest evidence of wide fluctuations in A1c values that are unrelated to

glycemic status among patient populations, resulting in patients being termed "low glycators" and "high glycators" (Rohlfing et al., 2002). In a study of over 4000 type 2 diabetics, Rodriguez-Segade et al. (2005) have shown a discrepancy between A1c control and the evolution of diabetic complications in patients with abnormal albumin values. The former report describes in detail a relatively complex relationship between A1c and plasma glucose. It points out that recent plasma glucose levels (within 3-4 weeks) contribute substantially more than earlier levels of A1c, confounding the description of an accurate and precise relationship. A further concern is that the official relationship has been determined from a limited number of samples in the first place and that short-term fluctuations in plasma glucose typical of type 1 diabetics cause discrepancies when A1c is estimated from just a few daily blood samples.

Another circulating protein that becomes glycated is apolipoprotein B, a component of low-density lipoproteins (LDL). This protein is of special interest because of its involvement in atherogenesis. Due to the short (3-5 day) circulating half-life of LDL, the glycated LDL level reflects mean glycemia over the preceding week (Lyons et al., 1986). A non-protein marker of potential use in monitoring short-term glycemic control is serum 1,5-anhydroglucitol (1,5-AG), which represents diabetic status over a 24-hr period because it reflects glucose's competitive inhibition of 1,5-AG reabsorption in the kidney tubule (Buse et al., 2003). The behavior of this marker is thus unique and has been used in Japan under the name GlycoMark™ for over a decade. However, because of changes in renal hemodynamics in normal pregnancies, it would not appear to be very useful in gestational diabetes.

Over the last 15 years, there have been many published reports describing the assessment of serum protein indicators, specifically fructosamine and glycated albumin, which assess glycemic status over an intermediate period – 2-3 weeks – reflecting the 14-20 day half-life of these molecules in serum. Fructosamine is the designated term for ketoamine formation from all glycated plasma protein collectively. Fructosamine testing was found to be easily automated and thus relatively inexpensive to perform. The use of fructosamine measurement as an intermediate index for glycation was the subject of an extensive FDA premarket evaluation in 1997 for an over-the-counter device manufactured by LXN Corporation of San Diego. Cefalu et al. (1999) demonstrated patient self-testing for fructosamine to be clinically equivalent to laboratory testing. During that period LXN Corp. was purchased by Inverness and subsequently by LifeScan, Inc., resulting in the termination of the commercial supply of home fructosamine testing strips in the midst of some interesting clinical studies. In subsequent years a diabetes screening project (Carter et al., 2000) and three clinical trials (Edelman et al., 2000; Carter et al., 2001; Lindsey et al., 2004) have demonstrated the potential for including an intermediary index for glycemia in clinically managing diabetes. A fructosamine screening test conducted by Carter and colleagues among work-place subjects demonstrated a 15% increase in detection of screening subjects with previously undiagnosed diabetes. The recent Lindsey study demonstrated glycemic improvement but no improvement in quality of life in diabetic subjects. These trial have coincided with a diminished interest in fructosamine monitoring as an adjunct to either blood glucose or A1c monitoring; with researchers concluding that it offered few advantages over A1c (Cembrowski, 1999).

The concept of an intermediate measurement for glycation, however, still intrigues many clinicians, especially those managing Type 2 diabetics whose glucose is relatively unregulated, and pregnant diabetics, who hope to fill the time gap between A1c and daily blood glucose monitoring. Experience with fructosamine testing has pointed out the potential value of an intermediate index to retrospectively evaluate changes in diet and exercise habits, possibly allowing faster evaluation of changes in medication dosages and other control measures, and to serve

as an inexpensive rapid screening test for impaired glycemic control (Carter, 2002). Albumin, the largest component of the plasma proteins (representing about 80% of the total), can now be reliably measured in the blood with fewer issues than fructosamine.

Structure of Glycated Albumin

Glycation of proteins in the blood occurs non-enzymatically following mass action kinetics, wherein free sugar condenses with certain reactive amino groups. Any reducing sugar can condense with protein amino groups, but since glucose is the principal carbohydrate nutrient in humans, it is the most important contributor to increased formation of glycated proteins associated with hyperglycemia in diabetes. Specifically, glycation is a post-translational modification event resulting from a reducing sugar (glucose) condensing with amino groups at N-terminus or on lysyl side chains (Cohen and Clements, 1999). So-called Amadori products are the principal forms in which circulating glycated proteins exist in vivo and assays to measure glycated proteins are designed to measure Amadori products. These products are described generally as ketoamines; or more technically as deoxyaminofructose. The measurement of the concentration of these compounds is the fructosamine measurement described previously.

In the 1980s two laboratory teams worked out the details of the structure of glycoalbumin, the most prevalent of the ketoamines. An understanding of what influences the glycation of individual proteins depends upon two facts: (1) the proportion of the total population of a particular protein carrying one or more glycated residues per molecule and (2) the number of glucose-modified sites per molecule of that particular protein. This relates to the pathophysiological process observed in human diabetics as well as to assay principles and methodological considerations. Each protein has a limited number of spots that can be targeted by glucose in vivo. Since human hemoglobin is 7.5% glycosylated, compared to 10-12% of normal human serum albumin, and since albumin has a much shorter half-life, the rate of nonenzymatic glycosylation of albumin in vivo is about nine times greater than that of hemoglobin (Garlick and Mazer, 1983).

In albumin, four lysine residues of a possible 59 candidates are known to undergo glycation in vivo, and one site (lysine-525) undergoes 33% of all glycation (Iberg and Fluckinger, 1986). There are five or six probable additional sites with minor amounts of glycation (Figure 1). The methodology for this study involves the isolation of albumin from diabetic blood, tritium labeling of glycosylation sites, tryptic digestion of protein into peptides, and isolation of tryptic peptides.

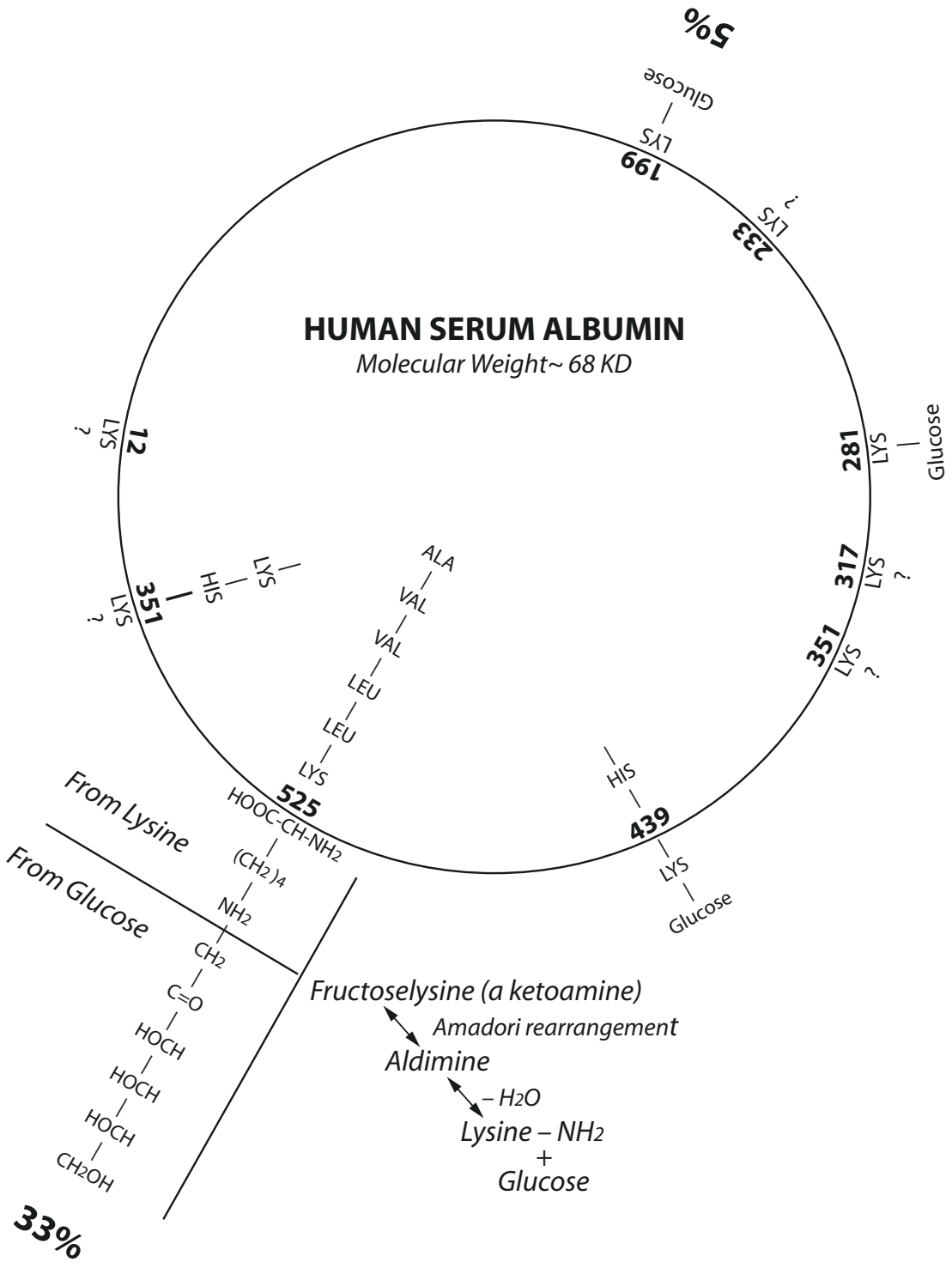
Methodology

In general, there are two methodological categories of testing employed to measure glycated protein in the blood. The first relies on charge differences to separate modified glucose from unmodified. Examples include ion exchange chromatography and electrophoresis. The second category exploits the presence of carbohydrate to distinguish glycated from nonglycated protein and includes affinity chromatography, immunoassay, and colorimetric procedures.

In the latter category, glycated albumin (GA) measurement often employs boronate affinity chromatography as a separatory technology. This technique can be utilized for a variety of assay methods, including immunoassay (Cohen and Hud, 1989; Hud and Cohen, 1989), radiochemical assay (Kato et al., 1989), or fluorescence assay (which may be quantified by spectrophotometry or albumin immunoassay). GA measurement may also be accomplished directly by immunoassay employing two different monoclonal antibody strategies. One involves making antibody to a common epitope, such as Amadori-modified GA (Ohe et al., 1987).

Figure 1: Glycated Albumin Molecule

4 confirmed major sites of non-enzymatic glycosylation in vivo
5 probable minor sites



The other involves making antibody to a unique epitope, such as borohydride-reduced GA (Cabre et al., 1994).

The definitive work that identified the nonenzymatic glycosylation sites of albumin in vivo employed affinity chromatography on phenylborate to isolate the peptides of interest and high performance liquid chromatography (HPLC) to resolve them (Shima et al, 1988). In this method albumin is separated from other serum proteins by differential elution in an ion exchange column. A second column separates glycated from non-glycated albumin by adsorption to boronate resin. The eluted albumin peaks were quantified by radioactivity in the original papers, but can also be detected with fluorescence monitors (Yasukawa et al., 1992). Semi-automated measurement of GA by affinity chromatography has been adapted to commercially available instruments. The nitroblue tetrazolium colorimetric reaction associated with the fructosamine assay has also been applied to GA measurement, and results are expressed in millimolar concentrations (Mashiba et al., 1992). In affinity chromatographic procedures, and in immunoassay with monoclonal antibodies specific to GA, results are expressed as percentage of total albumin that is glycated. The latter can also be expressed as nanomoles per milligram protein in immunoassays using antibodies to glucitollysine.

The techniques applied to the measurement of Apolipoprotein B (Apo B) of LDL are an example of the variety of methods available for extraction and separation of glycated protein. Originally done by ultracentrifugation and boronate affinity chromatography and relegated to a specialty laboratory, a plasma sample can now simply be subjected to agarose gel electrophoresis. In this instance increased electrophoretic mobility of plasma B-lipoprotein resulting from the greater electronegativity of glycation becomes a crude index of LDL glycation. In another approach, separation of glycated and nonglycated fractions can be performed by affinity chromatography on phenylboronate, with quantification of Apo B of both fractions accomplished by immunoradiometric assay. More elegantly, monoclonal antibodies can be made to react at specific sites with glycated Apo B epitopes within LDL. The application of these antibodies to an ELISA allows specific measurement of glycated LDL without any sample pretreatment (Cohen et al., 1993).

Although electrophoresis, boronate-affinity chromatography, and monoclonal antibody assays measure different properties, agreement between these assays is usually good. One exception is HPLC, which reported unusually high values most probably due to incomplete separation and sample size (Cohen, 1991).

A recently published test employs an enzymatic method for the rapid, efficient assay of glycated albumin (Yamaguchi et al., 2005), utilizing a dry chemistry system for monitoring. This system is intended for point of care (POC) testing and features a monitor combining two technologies: test tapes and strips and an optical analyzer. In this system a small sample volume of blood (20 uL) is exposed to three test tapes specific for GA%, ketoamine, and albumin in a temperature controlled environment. Changes of optical characteristics over time are evaluated via the test strip.

Advantages of Glycated Albumin Over A1c and Fructosamine

The kinetics of A1c, fructosamine (FA), and glycated albumin (GA) in response to blood glucose dynamics have been studied by Tahara and Shima (1995) and have been found to reflect the weighted mean of the preceding plasma level for 100, 40, and 30 days, respectively. When compared to hemoglobin A1c or fructosamine concentration, changes in GA have been found to have a closer correlation to changes in mean blood glucose in the first few weeks after intensification of insulin therapy in type 1 diabetics (Winocour et al., 1989). Glycated serum proteins were found to be more predictive (by multivariate analysis) of the standard deviation

of mean glucose levels than was glycohemoglobin in a study of both type 1 and type 2 patients who performed regular self-glucose monitoring over a 12-week period (Beisswenger et al., 1993). As with A1c, there is controversy in the literature as to whether FA assays should be corrected for serum protein concentration. However, Schleicher et al. (1993) demonstrated that GA measurements are inherently albumin concentration-compensated and thus relatively independent of high and low albumin states. Thus the presence of chronic renal disease does not influence measured GA, although metabolic acidosis has been reported to inhibit albumin glycation (Bordas-Fondrede et al., 1990) When compared to A1c and GA, fructosamine has been found by Shima et al. (1989) to be a poorer predictor of borderline diabetes and glucose tolerance test results. Kurashita et al. (1992) recommend glycated hemoglobin and GA as accurate measures of maternal glucose metabolism during pregnancy. Reports by Narayanan (1991) and Hicks et al. (2001) recommend glycated albumin for gestational diabetes monitoring.

In summarizing the abbreviated study of home fructosamine testing, Carter (2002) acknowledges that many healthcare scientists believe the FA assay to lack accuracy since it measures all glycated proteins. In addition, abnormally high lipid levels can interfere with the colorimetric assay, and it can be difficult to calibrate a baseline since the assay measures concentration only. Since the study found weekly fructosamine testing promising, the hope was for more acceptable medium-term markers to be developed for home use in the immediate future.

Application

Currently available methodology for measuring glycated albumin is complex as well as expensive and the test is generally relegated to laboratories. To make this technology available to both physicians and patients, it would be advantageous to develop a simple point-of-care (POC) assay with a reusable measuring device. The patent position of Epinex Diagnostics describes a rapid test for glycated albumin. Specifically, the patent describes a rapid immunochromatographic assay system with the capability of measuring both glycated albumin and total albumin in which a drop of blood is exposed to test strips and reagents in a measurement device that calculates and displays the test results as a percentage of glycated albumin to total albumin. The test as described requires 25–40 uL of blood to measure glycated albumin on one test strip and total albumin on the other by lateral flow immunochromatography. A measurement device then reads, calculates, and displays the percentage of glycated albumin result, an index referred to as G1A. In another embodiment of the invention, the test strips are coated with antibodies in the form of microparticles. Fluorescent tagging and a variety of test strip arrangements are also possible. The device offers data storage with potential linkage to the physician's office, a method of enhancing communication between patient and physician.

The Epinex device clearly offers the potential to be user friendly, convenient, fast, accurate within the range of clinical utilization, and inexpensive. Further, continuous and convenient feedback of data could offer the diabetic patient the advantage of monitoring their condition and modifying their treatment in coordination with their physician. Attractive aspects of adopting the G1A index include the promise of reducing the onset and severity of diabetic complications and making inroads on less invasive methods for monitoring patients, with a concomitant reduction in human and societal costs. Three arenas are envisioned for the G1A device: (1) physician's office tests, (2) rapid tests ordered by physicians, and (3) OTC self-testing. The intent behind the development of G1A is a diabetic monitoring index test to be recommended every four weeks.

Currently, no rapid test is available either to the physician or to the patient to screen for short-

to-medium term glycation. Self-monitoring blood glucose is indisputably a component of effective therapy for type-1 diabetics and for pregnant women taking insulin, with recommended sampling frequencies of three or more times daily. For type 2 diabetics, who represent about 80% of the diabetes population, the role of SMBG and frequency of testing are not clear, especially in diet-treated patients. In partnership with SMBG, the A1c test fulfills the role of long-term marker and predictor of clinical complications from diabetes. A recent article in the Los Angeles Times (19 May 2005) stated that two-thirds of the type 2 diabetics in the U.S. don't have tight control over their blood sugar levels. It further stated that 61% of type 2 diabetics surveyed, most of whom thought they were doing a good job controlling their blood sugar, don't know what the A1c test is. However, A1c is not yet accepted as a diagnostic tool and there are caveats concerning its long-term reliability vis a vis blood sugar levels in certain instances. The G1A test offers the potential for a new glycation index that can serve as a monitoring tool while complementing SMBG and A1c. It also suggests possible use as a diagnostic screening test for glycation, or to screen patients with mild-to-medium diabetic risk.

The Near Future

Applied diabetes research appears headed toward an emphasis on metabolic monitoring technologies that are less invasive or that rely on continuous blood or fluid sampling (Klonoff, 2002). The G1A index and other technologies being developed by Epinex Diagnostics are positioned to play a significant role in several areas. An intriguing body of literature dating from 1992 describes the nephropathic effects of glycated albumin associated with specific mechanisms via the mesangial cells, and abrogation of the biological effects of increased GA levels as a novel therapeutic approach to managing renal complications of diabetes (Bundschuh et al., 1992; Cohen et al., 1995; Chen et al., 2000; Yoo et al., 2004). Further, Schram et al. (2005) chronicles the association of glycation end products and increased pulse pressure in a large population of type 1 diabetics, suggesting another potential application of a reliable glycated protein test. The elegant monoclonal assay for ApoB would be a natural fit for Epinex technology, which could be applied to further exploring the relationship of ApoB to atherogenesis. Epinex is positioned to lead the way to a wider usage of the glycated albumin index in particular and rapid test analysis of glycated proteins in general. The adoption of these tests offers numerous possibilities to enhance the management of diabetes.

Epinex has commissioned an extensive survey of diabetologists, endocrinologists and diabetes researchers throughout the United States and internationally, to assess the familiarity of the diabetes care community with tests for intermediate glycation, and to explore further the potential applications for a rapid test for glycated albumin. The survey will provide a baseline for diagnostic procedures especially as they are currently applied to Type 2 diabetics. It will also test physician support for the use of an intermediate index for glycation as a component of diabetes management in a number of key areas, including gestational diabetes, geriatric monitoring, and undiagnosed or asymptomatic screening. The results of this survey will be published in the next issue of this monograph series.

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DCN-7401-1107-01