Review Article

Journal of Investigational Biochemistry
www.scopemed.org
DOI: 10.5455/jib.20140718044724

GESDAV

"Glycated albumin" a new paradigm in better monitoring Type 2 diabetes complications as a short-term glycemic index

Suresh Babu Kondaveeti[1], Anand Shaker Ivvala[1], R. Chidambaram[2]

[1]Department of Medical Biochemistry, Bharath University, Selayur, Chennai, Tamil Nadu, India, [2]Department of Radiology, Sri Lakshmi Narayana Institute of Medical Sciences, Affliated to Bharath University, Selayur, Chennai, Tamil Nadu, India

Address for correspondence:
Suresh Babu Kondaveeti, Bharath University, Selayur, Chennai, Tamil Nadu, India.
Phone: +91-9092580686,
E-mail: sureshbabu_kondaveeti@yahoo.com

Received: May 05, 2014
Accepted: July 18, 2014
Published: September 23, 2014

ABSTRACT

The metabolic disregulation of carbohydrates is the principal factor of diabetes, where high blood glucose levels persist which is the cause of diabetes complications, and that long-term control of blood glucose levels is required to avoid or lessen the damage caused by excess glucose. Monitoring blood sugar levels in individuals with diabetes mellitus is currently managed by a long-term testing. Albumin is the largest component of the plasma proteins, representing more than 80% of the total molecules and 60% of the total plasma protein concentration. It is replaced in the body approximately every 20-25 days, as there is a need of short-term marker glycated albumin (GA) will be the ideal marker for an intermediate index to measure glycation GA plays a double role in diabetes complications. In addition to being a marker for glycation, GA has been directly implicated for a role in several major complications of diabetes, including atherosclerosis, nephropathy, retinopathy and cognitive function. Levels of GA change more rapidly over time in response to changes in treatment than do levels of haemoglobin A1c (HbA1c). A recent survey of endocrinologists has demonstrated physician support for an intermediate index for glycemic control based on GA. With such a test available, doctors would recommend a substantial reduction in the level of self-monitoring blood glucose testing for their patients. The HbA1c test cannot effectively measure glycation within a 3-month period, during which time diabetes complications can advance if unchecked. There is a demonstrated need for an intermediate glycatio index to monitor diabetes. A test based on GA could provide a stable monthly index of glycemic control.

KEY WORDS: Glycated albumin, haemoglobin A1c, self-monitoring blood glucose, Type 2 diabetes

INTRODUCTION

Albumin is the most common protein found in serum, making up about 80% concentration of the circulating blood protein. It is replaced in the body approximately every 20-25 days. As with other proteins in the body, it is subject to non-enzymatic glycation by excess sugar. The glycation process is a condensation reaction between carbohydrate and free amino acid at the amino terminus of proteins or the epsilon amino groups of lysine residues of proteins. The reaction is initiated with attachment of the aldehyde function of acyclic glucose to a protein amino group via nucleophilic addition, forming an aldimine, also known as a Schiff base. This intermediate product subsequently undergoes an amadori rearrangement to form a 1-amino-1-deoxyfructose derivative in a stable ketoamine linkage, which in turn can cyclize to a ring structure [1]. Non-enzymatic glycation of albumin occurs at multiple sites, complex multi-step reactions ensue that cause formation of early and advanced glycation end-products (AGEs). AGEs lead to significant alterations in secondary structure and slight changes in tertiary structure of human serum albumin, resulting in the formation of thermodynamically more stable high molecular weight aggregates that may interfere with normal albumin function [2]. Protein glycation is both a marker for diabetes complications and an underlying cause of those complications. The purpose of diabetes monitoring is to help diabetics control the glycation. Diabetes is currently monitored by a combination of daily testing self-monitoring blood glucose (SMBG) and long-term testing haemoglobin A1c (HbA1c). A monthly diabetes monitoring test based on glycated albumin (GA) has the potential to provide better information for monitoring glycation. The progressive complications of unmanaged diabetes include heart disease, blindness, kidney failure, amputation of extremities due to circulation problems, and nerve disorders, as well as other chronic conditions. These complications are the cause of the immense personal, financial and societal costs of diabetes. Decades of research have established that prolonged exposure to excess glucose is the cause of diabetes complications and that long-term control of blood glucose levels is required to avoid or lessen the damage caused by excess glucose. The process of protein glycation

is now understood to be both a marker for the progress of diabetes complications and an underlying cause of many of the most serious complications. Excess glucose binds to proteins throughout the body, changing their shape and properties in ways that have been shown to cause damage to both the structure and function of body organs. It is, therefore, extremely important that blood glucose be kept at an acceptable level over time through diet, exercise, meal planning and medications (both insulin and other pharmaceutical agents such as glimepiride, metformin, used in diabetes control). Diabetics must control their levels of blood sugar (blood glucose) in order to manage their diabetes. To achieve this control, diabetics must monitor the way that sugars are being processed in their bodies. Serum proteins – proteins that circulate in the blood such as Hb or albumin – are among the proteins affected by the glycation process. Because glycation of serum proteins can be measured *in vitro*, diabetes monitoring has depended on the development and refinement of tests that indicate the level and progression of diabetes-related damage by measurement of serum protein glycation in a sample of blood.

Flowchart 1 shows the comparison of SMBG, glycated albumin and HbA1c Testing time period [3].

METHODOLOGIES OF GA ASSAY

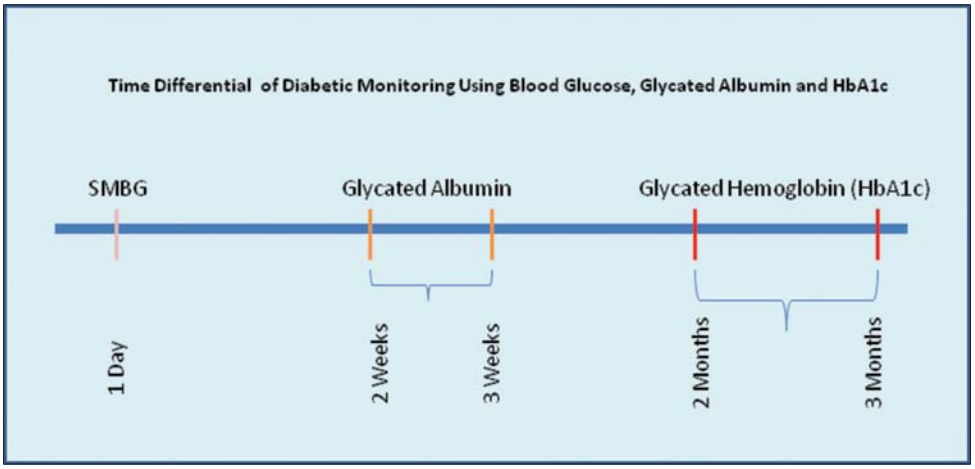
Several methods are presently employed in the isolation and quantification of GA. These include (a) enzymatic assay, (b) high-performance liquid chromatography and affinity chromatography, (c) immunoassay, including quantification by radio-immunoassay, (d) enzyme-linked immunosorbent assay, (e) enzyme-linked boronate immunoassay, (f) colorimetry, and (g) electrochemical. The enzymatic assay with a GA reference range of 14-16%.

GA and Its Role in Diabetes Complications

A link between glycated serum albumin and the disease processes of several of the complications associated with diabetes has been the subject of scientific and medical research for more than 10 years, and it has become clear that GA plays a dual role: As an indicator or marker of intermediate glycation, also as a causative agent of the damage of diabetes complications such as atherosclerosis, nephropathy and retinopathy.

Macrophages in the artery walls can recognize GA via specific receptors and, in turn, trigger activation of *endoplasmic reticulum kinase*, a potent cell-signaling pathway that activates NF kappa B, a key player in inflammatory reactions. This also produces potent cytokines like transforming growth factor (TGF) beta, the corollary being a perpetuation of the inflammatory pathways in the artery wall that characterizes the evolution of the atheroma plaque [4]. Recent clinical studies showed a significant correlation between increased serum GA level and the presence and severity of coronary artery disease (CAD) in patients with Type 2 diabetes mellitus and suggest the use of GA as a screening test for CAD [5]. *In vitro* studies indicate that GA in physiologically relevant concentrations possesses several pro-atherogenic effects which include promoting oxidative stress, production of inflammatory mediators, endothelial damage, and vessel wall hypertrophy [6]. GA undergo a variety of degradations, and rearrangements to form highly reactive carbonyl groups which are capable of reacting with other proteins to form intermolecular crosslinks which may eventually lead to vessel wall hypertrophy in the capillaries [7].

The functional changes seen in diabetic nephropathy may be the result of an increase in permeability of the glomerular basement membrane to glycated proteins. In the normal kidney, the transglomerular passage of serum proteins and macromolecules is highly selective due to the impermeability of glomerular basement membrane and distribution of molecular charge on the capillary wall, which results in the exclusion of some anionic proteins and proteins larger than 80 kDa in urine [8]. In diabetic nephropathy, there is an increase in the thickness of the glomerular basement membrane and the appearance of proteins larger than 100 kDa in urine. It has been proposed that glycosylation of serum albumin results in increased sequestration by endothelial vesicles, which may be a mechanism for trans endothelial transport across continuous endothelium *in vivo* [9]. The albuminuria and mesangial expansion that are known hallmarks of diabetic nephropathy can be generated by the interaction of GA with receptors in the mesangial cells,



Flow chart 1: Comparing SMBG, GA and HbA1c testing time period

independently of the direct actions of hyperglycemia. Through an amplification cell signaling cascade, involving protein kinase C and secretion of potent cytokines like TGF beta, a series of deleterious effects occur that produce glomerular dysfunction and albuminuria [10-12]. *In vitro* studies of human kidney, visceral epithelial cells show that GA inhibited nephrin synthesis through the engagement of the receptor for AGE-products and that nephrin loss and redistribution in glomeruli is present in patients with Type 1 and Type 2 diabetes [13]. The reduction of GA concentrations and/or blocking of its biologically active epitopes has demonstrated a beneficial influence in the pathogenesis of diabetic nephropathy [14].

A recent article on proliferative diabetic retinopathy discusses the involvement of GA in stimulating angiogenesis in the retina. Involvement of activator protein-1 (AP-1) has been implicated in both *in vitro* and *vivo* studies of angiogenesis. The study shows that GA stimulates the phosphorylation of c-Jun, a component of the transcriptional factor AP-1 in retinal glial cells. AP-1 up-regulates the mRNA level of cytokine vascular endothelial growth factor (VEGF), stimulating increased levels of VEGF and proliferation of unregulated capillary growth. When the newly formed capillaries invade the retina, leakage of blood plasma damages the retinal area, inducing macular degeneration. The result is a loss of vision in the central retinal area [15].

Correlation of GA and HbA1C as Glycemic Indices

Several recent studies have confirmed that point measurements of GA and glycated HbA1c are closely correlated, and that values for GA accurately represent the equivalent values for HbA1c in diabetic patients not subject to physiological conditions that disturb Hb metabolism. In these cases, GA has been found to be a better indicator of glycation than HbA1c. As expected, levels of GA change more rapidly over time in response to changes in treatment (as reflected by changes in fasting plasma glucose [PG]) than do levels of HbA1c.

The kinetics of HbA1 and GA in response to blood glucose dynamics have been studied and have been found to reflect the weighted mean of the preceding plasma level for 100, 40, and 30 days, respectively. When compared to HbA1c 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 [16].

A recent clinical study performed a comparison of GA and glycated Hb in Type 2 diabetic patients over 16 weeks. The study demonstrated that GA and HbA1c were significantly correlated in patients with Type 2 diabetes who had an HbA1c level below 7.5% with <0.5% variation for at least a year. The GA/HbA1c ratio displayed a normal distribution and the mean value of 2.9. The mean value did not differ among the 4 groups studied irrespective of their treatment for diabetes. When combined analysis of the four study groups was performed, GA and HbA1c showed a weak, but significant correlation [17]. The physiological and pathological conditions affecting GA compared GA and HbA1c levels in 209 diabetic patients whose glycemic control had been stable for at least the past 3 months. The results showed a strong correlation of HbA1c levels with GA levels in the study populations [18]. Another study evaluated the clinical utility of employing GA as an indicator of glycemia. Values of GA and HbA1c were compared to daily values of SMBG in 60 Type 1 patients and 50 Type 2 patients. Results show a very strong correlation of GA with HbA1c in Type 1 and Type 2 subjects. GA was also significantly correlated with maximum blood glucose in Type 1 and Type 2. The study concludes that the GA is a reliable indicator of average glucose levels in patients with Type 1 and Type 2 diabetes. This study also found a strong correlation of GA to pentosidine, an AGE product known to be a major cause of diabetic vascular complications in Type 1 and Type 2 diabetics, while HbA1c showed a correlation with Type 1 diabetics only [19]. A study measuring the clinical utility of an enzymatic method for the measurement of GA in plasma followed a sub-group of Type 2 diabetic patients for 18 weeks as they progressed from severe hyperglycemia (HbA1c ≥10.0%) toward better glycemic control, and the GA was better correlated with fasting PG than HbA1c for both groups of Type 2 diabetics (with good and poor control), and GA decreased more rapidly than HbA1c during intensive insulin therapy [20].

Clinical Utility of GA

Articles demonstrating the utility of GA as an alternative index to glycated Hb for diabetes control have been published for 25 years. As early as 1983, Jones *et al*. took note of the most rapid turnover of albumin as compared to Hb, and tested GA, HbA1c, and fasting blood glucose in newly diagnosed diabetes patients undergoing treatment. They found that GA decreased in step with fasting glucose over the initial 4 weeks of treatment, while HbA1c did not [21]. In (1989), Wincour determined that changes in GA had a closer correlation to changes in mean blood glucose in the first few weeks after intensification of insulin therapy in Type 1 diabetics when compared to HbA1c or fructosamine (FA) concentration [22]. Similarly, Wörner (1993) compared GA, glycated Hb and FA and concluded that GA gave the most precise data in medium term diabetic control [23].

More recently, published and unpublished studies in Japan, using a laboratory-based methodology for measuring GA, have confirmed the clinical utility of GA as a methodology for diabetes monitoring. A study of 18 Type 2 diabetic patients for 16 weeks as they progressed from untreated severe hyperglycemia (HbA1c ≥9.0%) to good glycemic control (HbA1c ≤6.5%) by intensive insulin treatment found that GA decreased more rapidly than HbA1c during intensive insulin therapy, but the percent reduction of HbA1c eventually corresponded with that of GA by 16 weeks after the start of treatment. This result demonstrates that GA provides a more responsive indication of therapeutic treatment than the HbA1c test [17]. A study performed at the Juntendo University School of Medicine, Japan, also demonstrated the effectiveness of using GA as an indicator to monitor diabetes therapy [24]. Another Japanese study tested whether GA was a more useful tool to monitor rapidly changing blood glucose than HbA1c. The study was performed on patients

hospitalized for diabetes control (51 men and 47 women). Patients were administered oral anti-diabetic drugs and 4-point SMBG tests daily. 7-point SMBG tests were done the 3rd and 10th hospital day, and the study concluded that GA measurement is more accurate for determining rapidly changing blood glucose than HbA1c due to the shorter half-life (10-14 days) of GA as compared to the half-life of HbA1c (2-3 months) [25]. There are few recent studies which reviewed the clinical utility of GA and its potential role as a short-term glycemic marker in controlling complications of diabetes [26,27]. The study carried by Furusyo *et al*. and Song *et al*. shows the role of GA in prediction of atherosclerosis in diabetic patients [28,29].

Survey Reports on Efficacy of GA as Short-term Glycemic Index Given By Various Endocrinologists

In September 2005, Epinex Diagnostics surveyed clinical and research endocrinologists and diabetes specialists about their current diagnostic practices for Type 2 diabetes patients and their opinion of the utility of a monthly test for glycation based on GA [30]. The company received a highly positive response to the product concept and technology from survey respondents. A six-page questionnaire was sent to more than 3500 endocrinologists and diabetes specialists, who collectively treat approximately 2.5 million diabetic patients, which constitutes approximately 20% of patients in the U.S. diagnosed with Type 2 diabetes.

A total of more than 3500 surveys was sent to a select group of endocrinologists, diabetes specialists, researchers, and general practitioners. 215 responses were received and evaluated, representing a margin of error from random survey sample calculations analysis of 6.5% at 95% confidence level. Virtually all the respondents treat diabetes patients on a regular basis, with the majority (54%) averaging 10 or more patients/day. Respondents indicated that current monitoring standards for diabetes involve a combination of SMBG procedure and A1C measurement. The survey indicated that Type 2 diabetes patients are most often asked to measure blood glucose twice (49%) or thrice (37%) daily for a total of (86%) [Figure 1] [31]. Compliant Type 2 patients on diet and medical maintenance, however, are asked to measure blood glucose twice daily (42%) and once (35%) daily, with only 11% indicating three or more times. Over 90% of respondents perform the A1C test 3-4 times/year in all diabetes patients. About 60% of respondents regard

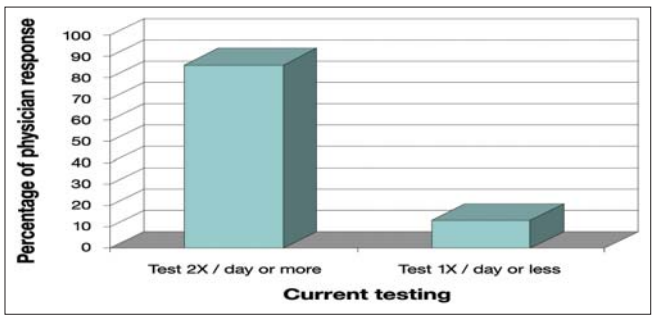


Figure 1: Endocrinologist survey - Recommendation for self-monitoring of blood glucose testing for Type 2 patients

the A1C test as the gold standard of diabetes management, but 31% note that it is occasionally misleading, and only approximately 12% encourage A1C over-the-counter (OTC) testing. Despite some obvious advantages associated with OTC and self-testing, including engendering patient empowerment, many physicians are concerned about the accuracy of OTC A1C tests.

The history of FA testing has served as a springboard to something better in intermediate glycemic control, judging from clinical test results and the overall response in this survey, in which 64% agreed there was a need for intermediate glycemic control and only 13% disagreed. The ability of FA to diagnose diabetes has been historically criticized [32-37] for yielding false positives and having a lack of sensitivity. In 1991, Narayanan summarized several potential interference agents for early FA assays [38], and a decade later, colorimetric determination of FA was criticized as being susceptible to interference factors in the blood, such as lipid [39]. At present, unreliable results appear because a collection of proteins, some of which vary rapidly and considerably during intercurrent disease, are being simultaneously assessed without the benefit of normal baseline data and a standardized relationship to total protein.

The concept of a rapid test in which the measurement of GA is compared to total albumin (glycation index: Percent of GA to total albumin) from a single drop of blood was explained to the survey respondents. Over half gave a favorable response to a test for short-to-intermediate glycemic status and control. Overall, 69% thought such a test would be very good for tracking gestational diabetes, and only 5% indicated not at all. When asked specifically about a GA index, 88% responded positively: 26% rated it excellent, 40% very good, and 22% good for tracking gestational diabetes. In addition, just over half of all respondents answered in the affirmative for GA monitoring geriatric patients. These patterns did not change when only the researchers 22% of survey respondents were considered. 73% of respondents envisioned a positive contribution for an OTC version of a rapid GA test. Included in this subtotal were 34% of the total respondents who viewed GA as complementary to A1C and finger stick glucose and another 18% who felt it would contribute to personal empowerment. According to the responses given by endocrinologists to the epinex survey, 13% of diabetes patients are asked to measure glucose once daily or less [Figure 1]. With the advent of a successful monthly GA test, 69% would be asked to measure glucose once or less daily [Figure 2]. This reduction of 56% from 86% to 30% in daily SMBG testing [Figure 2] [40] indicates the potential for a very large factor in healthcare savings. While the short-term information provided by SMBG is vital to all diabetes patients and cannot be replaced by GA, it is important to consider that diabetes management over the long-term should be improved by a more representative indicator of the disease processes involved. The highest percentage (38%) of respondents indicated that monthly GA status would relegate SMBG testing in compliant diabetes patients to once daily, and 50% would recommend a GA test ahead of fasting blood glucose or an oral glucose tolerance test for low-to-mid level diabetes risk patients

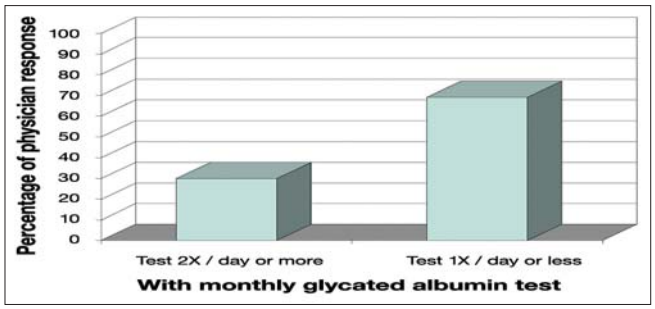


Figure 2: Endocrinologist survey - Recommendation for self-monitoring of blood glucose testing for Type 2 patients

It is clear from this survey that the establishment of a GA index for diabetes care has the potential to significantly impact diabetes monitoring as an adjunct to A1C and SMBG. It also represents an enormous potential saving in healthcare cost in that the survey results support a solid economic argument regarding a shift away from more expensive glucose testing in favor of a reliable and relatively inexpensive GA test.

Advantages of GA in Diabetes Monitoring of Hemodialysis, Cardiovascular Disease (CVD) and Gestational diabetes Patients

The significance of a comparison of GA with casual PG and HbA1c n was evaluated as an index of glycemic control in hemodialysis patients with Type 2 diabetes. A significant negative correlation was found between GA and serum albumin in diabetics on hemodialysis and multiple regression analysis led to the conclusion that GA testing estimates glycemic control in diabetic hemodialysis patients better than the HbA1c test, which leads to underestimation when erythropoietin is used (90% of dialysis patients) [41]. In another clinical study published in 2007, examination of patients with Type 2 diabetes revealed significant coronary stenosis in 237 out of 320 subjects. Serum GA and TNF-alpha levels were significantly higher in patients with CAD than in controls, and the study concluded that there is a strong and specific connection or association between elevated GA levels and coronary disease, with no correlation to HbA1c levels. The article suggested that testing for GA could provide a useful marker for predicting the onset of CAD in people with Type 2 diabetes.

A study conducted in Glasgow compared the respective value of serial measurements of GA, glycated plasma proteins (GPP), and HbA1c (glycated Hb), in early pregnancy in 14 insulin-dependent diabetic women the results demonstrate that measurement of GA or GPP gave an earlier indication to the clinician of improved diabetic control. The study also proposed that GA and GPP were less likely than HbA1c assays to be affected by non-diabetic conditions, such as patients who are anemic, received blood transfusions or were treated by hematinics [35]. Another study concluded that GA could be a better marker for glycometabolic control with respect to HbA1c in cases of pre-gestational diabetes (i.e., in pregnancy of Type 1 or Type 2 diabetic women) because of larger excursion of glycemic levels in these subjects, with respect to gestational diabetes pregnancies [42].

Factors are Effecting Current Diabetes Monitoring Methods

SMBG can only provide a snapshot of blood glucose levels and does not monitor glycation. Recent studies have shown no benefit to SMBG testing in improving glycemic control for Type 2 diabetics [20,43,44]. Studies reveal three areas of potential uncertainty exist in HbA1c testing such as biological variability [45-48], red blood cell variability [49-51], and clinical variability [52-54].

Disadvantages of GA Estimation

Unfortunately, there may also be interferences with the GA assay. While HbA1c measurement is affected by reduced erythrocyte survival or an increase in young erythrocytes (e.g., during treatment with erythropoietin-stimulating agents), GA can be influenced by factors that affect albumin turnover [55-57]. Because the majority of patients with advanced nephropathy have overt proteinuria, GA values may also be affected in these patients. One study has shown this to be the case; there was a significant decrease in GA values independent of glycemic state in diabetic patients with nephritic syndrome, while nonnephrotic range proteinuria did not significantly influence GA [58].

Research Status of GA Testing in India

India is facing an epidemic of diabetes. At present, confirmed diabetes patients in India are 67 million, with another 30 million in pre-diabetes group. By 2030, India will have the largest number of patients in the world [59]. A study carried out by the Diabetes Research Centre, WHO Collaborating Centre for Research, Education and Training in Diabetes, Chennai-India concluded that GA may be a useful marker for assessing short-term glycemic changes in patients with Type 2 diabetes. It may be useful to assess the early improvement in the treatment of diabetes [60,61]. Another study carried out in South Indian diabetic population concludes that the persistent increase in GA and microalbuminuria may be considered as risk markers in diabetic nephropathy. Therefore, regular screening for microalbuminuria and estimation of GA can help in the clinical management, to prevent complications [62]. Similarly another study evaluates the levels of GA along with microalbuminuria in diabetic retinopathy patients concludes that there is a significant relation between duration of diabetes, GA levels and diabetic retinopathy [63]. The relation between dyslipidemia and GA explained by another study which concludes that GA levels quicker response to short-term changes in diabetes treatment and glycemic control index as well as for early diagnosis of dyslipidemia [64].

CONCLUSION

Given the expanding diabetes population, endocrinologists increasingly recognize the need for an intermediate glycemic

indicator. A GA test has the potential to significantly impact diabetes monitoring and fulfill this need. With a turnover time in plasma of 2-3 weeks, GA provides a glycation update on a monthly basis. GA has been shown to be more accurate than the existing A1C "gold standard" for diabetes patients undergoing hemodialysis, a major segment of the diabetes population. Levels of GA have also been shown to have a substantial relationship to certain types of diabetes complications such as nephropathy, retinopathy and CVD. With more and more studies questioning SMBG as an effective method for monitoring Type 2 diabetes, GA has the potential to provide a reliable and effective alternative. It has already been recognized as an ideal marker for gestational diabetes, with potential clinical applications for diabetes patients undergoing hemodialysis and diabetes patients with CVD. An available GA rapid test as a monthly indicator of glycation could bring about a significant reduction in daily SMBG, resulting in substantial healthcare cost savings as well as an increase in patient compliance. Availability of such a test to the patient depends on reconciling the disparate results seen with various measurement methodologies. There is currently no rapid GA test for intermediate glycation available to physicians or patients.

REFFERENCES

1. Cohen MP. Treatment of complications of diabetes with substances reactive with the fructyosyl-lysine structure in glycated albumin. U.S. Patent No. 1994, 5,518,720.
2. Iberg N, Flückiger R. Nonenzymatic glycosylation of albumin *in vivo*. Identification of multiple glycosylated sites. J Biol Chem 1986;261:13542-5.
3. Available from: http://www.biomarkerbliti.org/articles/6?print=true. [Last accessed on 2014 Apr 13].
4. Hattori Y, Suzuki M, Hattori S, Kasai K. Vascular smooth muscle cell activation by glycated albumin (Amadori adducts). Hypertension 2002;39:22-8.
5. Pu LJ, Lu L, Shen WF, Zhang Q, Zhang RY, Zhang JS, *et al*. Increased serum glycated albumin level is associated with the presence and severity of coronary artery disease in type 2 diabetic patients. Circ J 2007;71:1067-73.
6. Cohen MP, Ziyadeh FN, Chen S. Amadori-modified glycated serum proteins and accelerated atherosclerosis in diabetes: Pathogenic and therapeutic implications. J Lab Clin Med 2006;147:211-9.
7. Brownlee M, Pongor S, Cerami A. Covalent attachment of soluble proteins by nonenzymatically glycosylated collagen. Role in the *in situ* formation of immune complexes. J Exp Med 1983;158:1739-44.
8. Cohen MP, Ziyadeh FN, Lautenslager GT, Cohen JA, Shearman CW. Glycated albumin stimulation of PKC-beta activity is linked to increased collagen IV in mesangial cells. Am J Physiol 1999;276:F684-90.
9. Thomas MC, Tikellis C, Burns WM, Bialkowski K, Cao Z, Coughlan MT, *et al*. Interactions between renin angiotensin system and advanced glycation in the kidney. J Am Soc Nephrol 2005;16:2976-84.
10. Ziyadeh FN, Han DC, Cohen JA, Guo J, Cohen MP. Glycated albumin stimulates fibronectin gene expression in glomerular mesangial cells: Involvement of the transforming growth factor-beta system. Kidney Int 1998;53:631-8.
11. Bohrer MP, Deen WM, Robertson CR, Troy JL, Brenner BM. Influence of molecular configuration on the passage of macromolecules across the glomerular capillary wall. J Gen Physiol 1979;74:583-93.
12. Williams SK, Siegal RK. Preferential transport of non-enzymatically glucosylated ferritin across the kidney glomerulus. Kidney Int 1985;28:146-52.
13. Doublier S, Salvidio G, Lupia E, Ruotsalainen V, Verzola D, Deferrari G, *et al*. Nephrin expression is reduced in human diabetic nephropathy: Evidence for a distinct role for glycated albumin and angiotensin II. Diabetes 2003;52:1023-30.
14. Cohen MP, Sharma K, Jin Y, Hud E, Wu VY, Tomaszewski J, *et al*. Prevention of diabetic nephropathy in db/db mice with glycated albumin antagonists. A novel treatment strategy. J Clin Invest 1995;95:2338-45.
15. Okumura A, Mitamura Y, Namekata K, Nakamura K, Harada C, Harada T. Glycated albumin induces activation of activator protein-1 in retinal glial cells. Jpn J Ophthalmol 2007;51:236-7.
16. Tahara Y, Shima K. Kinetics of HbA1c, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. Diabetes Care 1995;18:440-7.
17. Takahashi S, Uchino H, Shimizu T, Kanazawa A, Tamura Y, Sakai K, *et al*. Comparison of glycated albumin (GA) and glycated hemoglobin (HbA1c) in type 2 diabetic patients: Usefulness of GA for evaluation of short-term changes in glycemic control. Endocr J 2007;54:139-44.
18. Koga M, Matsumoto S, Saito H, Kasayama S. Body mass index negatively influences glycated albumin, but not glycated hemoglobin, in diabetic patients. Endocr J 2006;53:387-91.
19. Yoshida N, Okumura K, Aso Y. High serum pentosidine concentrations are associated with increased arterial stiffness and thickness in patients with type 2 diabetes. Metabolism 2005;54:345-50.
20. Paroni R, Ceriotti F, Galanello R, Battista Leoni G, Panico A, Scurati E, *et al*. Performance characteristics and clinical utility of an enzymatic method for the measurement of glycated albumin in plasma. Clin Biochem 2007;40:1398-405.
21. Jones IR, Owens DR, Williams S, Ryder RE, Birtwell AJ, Jones MK, *et al*. Glycosylated serum albumin: An intermediate index of diabetic control. Diabetes Care 1983;6:501-3.
22. Winocour PH, Bhatnagar D, Kalsi P, Hillier VF, Anderson DC. A comparison of direct measures of glycaemia and glycated blood proteins in insulin-dependent diabetes mellitus. Clin Biochem 1989;22:457-61.
23. Wörner W, Pfleiderer S, Rietbrock N. Selective determination of non-enzymatic glycosylated serum albumin as a medium term index of diabetic control. Int J Clin Pharmacol Ther Toxicol 1993;31:218-22.
24. Kawamori R. Insulin resistance seen in non-insulin dependent diabetes mellitus and hypertension. Hypertens Res 1996;19 Suppl 1:S61-4.
25. Tamemoto H, Toyoshima H, Saitoh T, Yuzawa M, Yuzawa M, Ishikawa S, *et al*. Efficacy of glycoalbumin to monitor rapidly changing blood glucose. ADA 2007;Suppl 3:25-32. Abstract
26. Furusyo N, Hayashi J. Glycated albumin and diabetes mellitus. Biochim Biophys Acta 2013;1830:5509-14.
27. Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker. Endocr J 2010;57:751-62.
28. Furusyo N, Koga T, Ai M, Otokozawa S, Kohzuma T, Ikezaki H, *et al*. Plasma glycated albumin level and atherosclerosis: Results from the Kyushu and Okinawa Population Study (KOPS). Int J Cardiol 2013;167:2066-72.
29. Song SO, Kim KJ, Lee BW, Kang ES, Cha BS, Lee HC. Serum glycated albumin predicts the progression of carotid arterial atherosclerosis. Atherosclerosis 2012;225:450-5.
30. Available from: http://www.epinex.com/newsletter/Epinex_Newsletter4.pdf. [Last accessed on 2014 Apr 13]
31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769832/figure/fig1/. [Last accessed on 2014 Apr 13]
32. Baker JR, O'Connor JP, Metcalf PA, Lawson MR, Johnson RN. Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. Br Med J (Clin Res Ed) 1983;287:863-7.
33. Shima K, Abe F, Chikakiyo H, Ito N. The relative value of glycated albumin, hemoglobin A1c and fructosamine when screening for diabetes mellitus. Diabetes Res Clin Pract 1989;7:243-50.
34. Guillausseau PJ, Charles MA, Paolaggi F, Timsit J, Chanson P, Peynet J, *et al*. Comparison of HbA1 and fructosamine in diagnosis of glucose-tolerance abnormalities. Diabetes Care 1990;13:898-900.
35. Tsuji I, Nakamoto K, Hasegawa T, Hisashige A, Inawashiro H, Fukao A, *et al*. Receiver operating characteristic analysis on fasting plasma glucose, HbA1c, and fructosamine on diabetes screening. Diabetes Care 1991;14:1075-7.
36. Kasezawa N, Kiyose H, Ito K, Iwatsuka T, Kawai H, Goto Y, *et al*. Criteria for screening diabetes mellitus using serum fructosamine level and fasting plasma glucose level. The Japanese Society of Multiphasic Health Testing and Services (JMHT), Fructosamine Working Committee. Methods Inf Med 1993;32:237-40.

37. Cefalu WT, Ettinger WH, Bell-Farrow AD, Rushing JT. Serum fructosamine as a screening test for diabetes in the elderly: A pilot study. J Am Geriatr Soc 1993;41:1090-4.
38. Narayanan S. Laboratory monitoring of gestational diabetes. Ann Clin Lab Sci 1991;21:392-401.
39. Carter AW. Home fructosamine testing: Is its demise premature? Diabetes Technol Ther 2002;4:643-4.
40. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769832/figure/fig2/. [Last accessed on 2014 Apr 13]
41. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, *et al.* Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: Effect of anemia and erythropoietin injection. J Am Soc Nephrol 2007;18:896-903.
42. Leiper JM, Talwar D, Robb DA, Lunan CB, MacCuish AC. Glycosylated albumin and glycosylated proteins: Rapidly changing indices of glycaemia in diabetic pregnancy. Q J Med 1985;55:225-31.
43. Davis WA, Bruce DG, Davis TM. Does self-monitoring of blood glucose improve outcome in type 2 diabetes? The Fremantle Diabetes Study. Diabetologia 2007;50:510-5.
44. Schütt M, Kern W, Krause U, Busch P, Dapp A, Grziwotz R, *et al.* Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 Centers in Germany and Austria. Exp Clin Endocrinol Diabetes 2006;114:384-8.
45. Franciosi M, Pellegrini F, De Berardis G, Belfiglio M, Cavaliere D, Di Nardo B, *et al.* The impact of blood glucose self-monitoring on metabolic control and quality of life in type 2 diabetic patients: An urgent need for better educational strategies. Diabetes Care 2001;24:1870-7.
46. Thoolen BJ, de Ridder DT, Bensing JM, Gorter KJ, Rutten GE. Psychological outcomes of patients with screen-detected type 2 diabetes: The influence of time since diagnosis and treatment intensity. Diabetes Care 2006;29:2257-62.
47. Jeffcoate SL. Diabetes control and complications: The role of glycated haemoglobin, 25 years on. Diabet Med 2004;21:657-65.
48. Kasayama S, Morita S, Saito H, Mikio M, Koga M. Glycated hemoglobin, but not serum glycated albumin, is influenced by erythrocyte and iron metabolism indices in pre-menopausal women. ADA Abstract, 2007.
49. Gould BJ, Davie SJ, Yudkin JS. Investigation of the mechanism underlying the variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. Clin Chim Acta 1997;260:49-64.
50. Rendell M, Stephen PM, Paulsen R, Valentine JL, Rasbold K, Hestorff T, *et al.* An interspecies comparison of normal levels of glycosylated hemoglobin and glycosylated albumin. Comp Biochem Physiol B 1985;81:819-22.
51. Hudson PR, Child DF, Jones H, Williams CP. Differences in rates of glycation (glycation index) may significantly affect individual HbA1c results in type 1 diabetes. Ann Clin Biochem 1999;36:451-9.
52. Madsen H, Ditzel J. Changes in red blood cell oxygen transport in diabetic pregnancy. Am J Obstet Gynecol 1982;143:421-4.
53. Szwergold BS, Howell SK, Beisswenger PJ. Intracellular nonenzymatic glycation of hemoglobin in human erythrocytes is controlled by enzymatic deglycation mechanisms. Diabetes 2003;52 Suppl 1:A190. [Abstract #815].
54. Schnedl WJ, Liebminger A, Roller RE, Lipp RW, Krejs GJ. Hemoglobin variants and determination of glycated hemoglobin (HbA1c). Diabetes Metab Res Rev 2001;17:94-8.
55. Holmes E, Ersahin C, Augustine G, Gryzbac M, Murrell J, McKenna K, *et al*. Glycated albumin low in obese, type 2 diabetic patients. AACC Conference Abstract; 2006.
56. Miyashita Y, Nishimura R, Morimoto A, Matsudaira T, Sano H, Tajima N. Glycated albumin is low in obese, type 2 diabetic patients. Diabetes Res Clin Pract 2007;78:51-5.
57. Koga M, Otsuki M, Matsumoto S, Saito H, Mukai M, Kasayama S. Negative association of obesity and its related chronic inflammation with serum glycated albumin but not glycated hemoglobin levels. Clin Chim Acta 2007;378:48-52.
58. Koga M, Murai J, Saito H, Matsumoto S, Kasayama S. Effects of thyroid hormone on serum glycated albumin levels: Study on non-diabetic subjects. Diabetes Res Clin Pract 2009;84:163-7.
59. Okada T, Nakao T, Matsumoto H, Nagaoka Y, Tomaru R, Iwasawa H, *et al.* Influence of proteinuria on glycated albumin values in diabetic patients with chronic kidney disease. Intern Med 2011;50:23-9.
60. Times of India, Diabetes epidemic on the rise in India, 2013. Available from: http://www.timesofindia.indiatimes.com/life-style/health-fitness/health/Diabetes-epidemic-on-the-rise-in-India/articleshow/25758884.cms. [Last accessed on 2014 Apr 13]
61. Satyavani K, Priyanka T, Vishwanath V. Efficacy of glycated albumin (GA) in comparison with glycated haemoglobin (HbA1c) in type 2 diabetic subject in India. JK Sci J Med Educ Res 2011;13:1-5.
62. Kondaveeti SB, DK, Mishra S, Kumar RA, Shaker IA. Evaluation of glycated albumin and microalbuminuria as early risk markers of nephropathy in type 2 diabetes mellitus. J Clin Diagn Res 2013;7:1280-3.
63. Kondaveeti SB, Kumar RA, Shaker IA. Glycated albumin and microalbuminuria as risk factors in diabetic retinopathy of type 2 diabetis mellitus. J Biol Sci Opinion 2013;1:1-4.
64. Kondaveeti SB, Shaker IA, Kumar RA, Palwan H, Raja G. Evaluation of glycated albumin and dyslipidemia in type 2 diabetes mellitus. Int J Bioassays 2012;01:112-5.

Source of Support: Nil, Conflict of Interest: None declared.