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Case Series

Glycated Albumin- A possible choice of marker for early diagnosis of Pre-diabetes

Rajeev Kumria[1]*, Shilpa Raina[1], Athira Sasidharan[2], Ramesh Bhaskaran[2]

[1]Dept. of Biochemistry, Shri Venkateshwara University, Gajraula, Uttar Pradesh, India
[2]Jubilee Mission Medical College and Research Institute, Thrissur, Kerala, India

Abstract

Diabetes has emerged as a major challenge worldwide with the number of Diabetics and pre-diabetics growing at an alarming pace. While more is being understood about the long-term impacts and the pathophysiology of diabetes related complications such as Diabetic retinopathy, Diabetic Kidney Disease, Cardio-metabolic changes, more understanding is needed for a goal directed management program to prevent the descent towards these complications. The obvious approach would be to catch the diabetics while still in their pre-diabetes phase. While both HbA1c and fasting plasma Glucose levels have served well over time, it is now imperative that more exploration is needed to find biomarkers for different clinical purposes and phases in managing Diabetes. There are situations in which HbA1c and FGP do not serve as the best markers due to other underlying conditions which directly impact the biochemistry of these biomarkers. Conditions that shorten erythrocyte life cycle, conditions like anemia directly impacting Hemoglobin level will directly impact the level of HbA1c. Under all these conditions HbA1c will not be an ideal biomarker for diagnosis of pre-diabetes, diabetes and monitoring of long term glycemic control. Some other candidate biomarkers for the intermediate term glycemic control are Fructosamine and Glycated Albumin; both are constituents of Advanced Glycation end products. While both have shown promise in several studies Glycated Albumin a key constituent of Fructosamine is better in terms of assay standardization, assay automation and clinical deployment. Another big advantage of Glycated Albumin is that the rate of Glycation is nearly four (4) times higher than that of HbA1c making it much more sensitive to adverse changes in long term Glycemic Control. As Albumin has a turnover of 4-5 weeks, Glycated Albumin works to ascertain intermediate term Glycemic Control of 2-3 weeks or a month at the most. This is useful in many scenarios where therapeutic dose adjustment is needed. It is also important to catch the diabetics young as the longer life expectancy, increasing incidence of diabetes predisposes a large section of diabetics to long-term diabetic complications like retinopathy, kidney disease, neuropathy diabetic foot etc., this puts a grave stress on the patient as well as the healthcare system. Glycated Albumin holds lot of promise as a Biomarker for Pre-diabetes diagnoses due to its sensitivity compared to HbA1c. Glycated Albumin can also be deployed in all cases where HbA1c may not be an ideal candidate for monitoring glycemic control. A new consensus needs to emerge on the selection of optimal biomarkers for diabetes. This paper aims to research and summarize the available information and data on Glycated Albumin's utility in diabetes and pre-diabetes management.

Keywords: World Health Organization (WHO), Glycated Albumin, Cardiovascular disease (CVD)

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1. Introduction

Diabetes Mellitus or Non Insulin Dependent Type 2 Diabetes is on an upsurge in the past few decades. The typical presentation is being marked by comparatively earlier onset due to changing lifestyles thereby affecting young and productive population world over. The characteristic clinical presentation of Type 2 diabetes is marked by higher Body Mass Index (BMI), sedentary lifestyles, consumption of processed food high in carbohydrates and various syrups leading to insulin resistance. The scientific and medical community is now understanding the longitudinal metabolic complications of insulin resistance such as retinopathy, hypertension, cardio-metabolic complications, diabetic foot, diabetic kidney disease and many others.[1] The question that is often asked is whether the quest for diabetes markers is over with the settlement of HbA1c values and their wider acceptance globally. Glycogenesis ensue once Insulin binds to its receptor. This leads to the conversion of excessive cytosolic glucose to Glycogen and initiates the process of lipogenesis from excessive cytosolic acetyl-COA. Glucagon hormone is an antagonist of these mechanisms.[2]. Normal or lower blood glucose levels remains in the blood and does not readily enters the cell. Connections between glycated proteins such as glycated albumin have been found with

*Corresponding author: Rajeev Kumria
Email: rajeev.kumria@gmail.com

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diabetic complications with more clarity and emphatic evidence in the DCCT/EDIC study.[3]

1.1 Epidemiology

India is often referred to as the diabetes capital of the world. India has around 77 million people diagnosed and living with active Diabetes. Another 136 million in pre-diabetes stages.[4]On a global level almost 592 million individuals may be touched by diabetes and related complications by 2035.[5] It is estimated that in the next few decades the prevalence rate might increase by as much as 55%.[6] The problem has become one with humongous proportions and requires solutions that can positively impact the long-term outcome of Diabetes in a very large subset of global population. **Table 1**

Asian Indians along with Native Americans and Pacific Islanders have the higher propensity of developing type 1 diabetes mellitus.[7] The long-term complications of Diabetes when seen in perspective with the numbers make the picture even more scary. At the current rate of growth in Diabetes if a fraction of these proceed towards complications like Retinopathy, Diabetic Kidney disease, Diabetic foot and other neuropathies then we are looking at an exceedingly large number of people with severe complications putting all sorts of stress on the healthcare system, society and the individual.

1.2 Diagnostic criterion

As per the World Health Organization (WHO) the classification is as follows

A. Clinical stages: Normoglycaemia, Impaired glucose tolerance/impaired fasting glucose (IGT/IFG), diabetes.

B. Etiological types: Gestational impaired glucose tolerance (GIGT) and GDM: fasting glucose = 7.0 mmol/L (126 mg/dL) and/or 2-h glucose = 7.8 mmol/L (140 mg/dL) after a 75-g OGTT.[8]

ADA follows the following criterion for diagnosis

A. HbA1c ≥6.5%: DCCT standardized assay method with NGSP certification

B. Fasting* (8 hours fasting) Plasma Glucose ≥126 mg/dL (7 mmol/L).

C. WHO prescribed methodology of Oral Glucose Tolerance Test wherein a 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L).[9]

Elevated Glucose levels in the blood will lead to Glycation of a variety of biomolecules. Collectively these are known as Advanced Glycation End products. HbA1c is one such glycation end products which has been deployed as marker of long term Glycemic control and monitoring.[10] These glycated proteins were studied for their physico-chemical properties and to understand the mechanistic pathways of Glycation.[11]This family of Glycated Proteins are always of interest as potential biomarkers of Glycemic control as well myriad other applications such as Alzheimers, Metabolomics, gerontology and senescence and Diabetic complications stemming out of poor long term glycemic control.

1.3 Diabetes complications: Pathophysiology and implications

A vast majority of the burden is of non-insulin dependent type 2 diabetes mellitus which is characterized by insulin resistance in peripheral tissue leading to poor uptake of blood glucose. Where as type 1 or insulin dependent diabetes is characterized by impaired insulin production by body. Before the actual decline of insulin secretory capabilities of islet of Langerhans, compensatory hypersecretion of insulin from the pancreatic islets may ensue. This leads to marked impact on all those organs which are actively involved in either uptake or metabolism of Glucose like skeletal muscles, liver, adipose tissue.[12] Elevated fatty acid levels in conjunction with proinflammatory cytokines cause a cascade of events that result in insulin resistance leading to impaired glucose transport and increased lipid breakdown. Interestingly the sub-optimal production of insulin leads of production of increasing levels of glucagon. This leads to a further elevation in blood Glucose level.[13]

Two types of changes cause the gross angiopathy in Diabetes and these are Microvascular (damage to smaller vessels) and macrovascular (damage to larger vessels). Both these changes lead to different outcomes and pathological events (**Table 2**).

Microvascular disease tends to occur in kidneys, retina and vascular endothelium as the glucose uptake is not directly dependent on insulin activity. Elevated glucose levels or hyperglycaemia leads to damage of endothelium, increased superoxide production causing increased oxidative stress. The continuous hyperglycemic state in body ultimately leads to enhanced glycation and the production advanced glycation end-products. All this leads to development of disease as described above,[14]

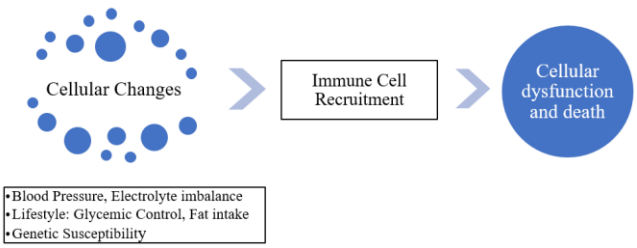

Figure 1: Areas leading to long term diabetic complications

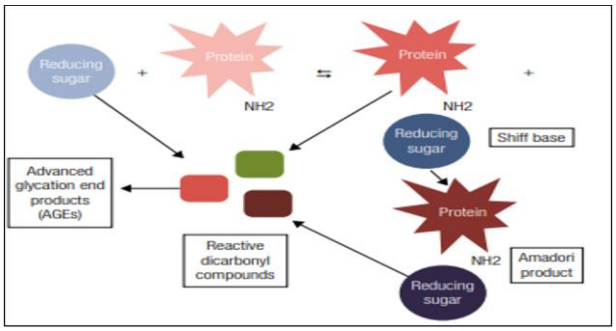

Figure 2: Schematic on the process of Glycation of proteins

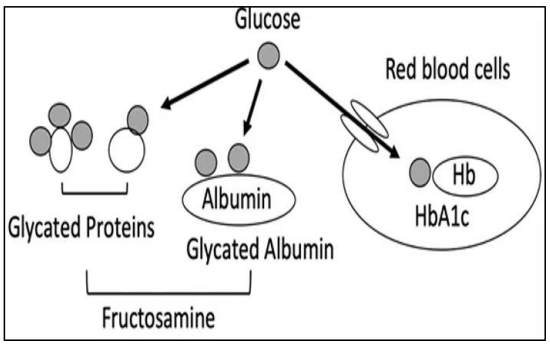

Figure 3: Fructosamine and glycated albumin in blood

Table 1: Diabetic burden in south east asia: Source IDF Atlas 2021.

	Year		
	2019	**2030**	**2045 (Estimates)**
Diabetes Prevalence data			
Prevalence in SEA	8.7%	9.6%	11.3%
Comparative prevalence (Age adjusted)	10.0%	10.9%	11.3%
People living with Diabetes (number)	90 m	113.3m	151.5m
Deaths due to Diabetes (number)	747,000	-	-
Healthcare expense in adult population due to diabetes			
Total healthcare expenditure, ($)	10.1 b	12.1b	15.0b
Adults with Impaired glucose tolerance			
Prevalence in SEA	4.5%	4.9%	5.7%
Comparative prevalence (Age adjusted)	5.4%	5.7%	5.8%
People living with IGT (number)	46.9m	58.5m	76.6m
Adults with Impaired fasting glucose			
Prevalence in SEA	9.2%	9.2%	9.4%
Comparative prevalence (Age-adjusted)	8.8%	9.2%	9.3%
People living with impaired fasting glucose	95.2m	109.4m	125.4m
Estimated adults with Undiagnosed diabetes (20-79 years)			
Regional prevalence	51.2%	-	-
Number of people with undiagnosed diabetes	46.2m	-	-

Table 2: Diabetic complications stemming from vascular changes

Type of Vascular change	**Microvascular**	**Macrovascular**
Pathology	Retinopathy, Nephropathy, Neuropathy.[53]	Cardiovascular, Cerebrovascular (Strokes), Depression, Dementia, Sexual Dysfunction.[54]

Table 3: Comparison of assay methods for HbA1c

Assay	**Method**	**Pro**	**Con**
Ion Exchange Chromatography	Differential mobility of HbA1c based on Isoelectric point	Hb Variants analysis is possible. High Precision	Hemoglobinopathies, HbF, Carbamylated Hb interferences

Boronate Affinity	Binding of Glucose and m-aminophenylboronic acid	No interferences	Lacks Specificity towards. Measures other glycation sites on ß and α chains
Immunoassays	Specific Antibodies to Glucose and 4-10 N terminal amino acids of ß chain	No interferences. Can be conducted on routine clinical chemistry analyzers in clinical labs	Affected by Hemoglobinopathies, HbF interference

Table 4: A comparison of glycated proteins in diabetes monitoring

Analyte	**HbA1c**	**Glycated albumin**	**Fructosamine**
Glycosylation	Glycated valine of N-terminal the ß-chain of hemoglobin	Glycated lysine of Albumin	Fructosamine of Serum proteins
Location	Red Blood Cell	Whole Body	Whole Body
Units of Measurement	%, mmol/mol	%, mmol/mol	µmol/l
Duration of Glycemia measurement	Long 2-3 months	Intermediate (2-3 weeks)	Intermediate (2-3 weeks)
Strengths	ADA, UKPDA, IDA standard for monitoring and diagnosis of Diabetes, Low with-in person variability	Monitoring the effects of changes in therapy, Pregnancy, Dialysis, Hemoglobinopathies, Iron Deficiencies, Anemias, Low with-in person variability	Monitoring the effects of changes in therapy, Pregnancy, Dialysis, Hemoglobinopathies, Iron Deficiencies, Anemias
Limitations	Short term monitoring, Hemoglobinopathies, Iron Deficiencies, Anemias, hemodialysis, pregnancy	Nephrosis, Liver Cirrhosis, Thyroid Disease	Poor standardization data, Lack of substantive evidence, Affected by serum protein concentration and proportion, Nephrosis, Liver Cirrhosis, Thyroid disease

2. Review of Literature

A study was performed looking at the various available literature to review the potential, opportunities and challenges associated with using advanced and intermediate glycated end products as markers for Diabetes monitoring and whether there could be a case for updating the current diagnostic algorithm to include more suitable biomarkers. The review is limited to studying the impact of elevated plasma Glucose on Glycation and how some of these Glycation end products which can be candidates for Diabetes screening and monitoring along with established criterion of FPG, HbA1c, OGTT. The Glycated proteins under focus are Glycated Albumin, Fructosamine and HbA1c with a special focus on the limitations of HbA1c. The study also looks at the possibility of other Glycated Proteins such as Glycated albumin being potentially. A lot is known about HbA1c and we wanted to place other Glycated Protein biomarkers together to ascertain the how this addresses the challenges of Diabetes Diagnosis and Monitoring.

2.1. The Glycation process and its end products

Proteins that become glycated due to exposure to sugars are known as glycation end products.[15] These glycation end products or advanced glycation end products provide valuable pathological information and act as biomarkers in a variety of longitudinal consequences such as aging, degenerative diseases, diabetes, atherosclerosis, chronic kidney disease, and Alzheimer's disease. In atherosclerosis the implications of AGE's has been widely studied.[16] The process of Glycation involves the lysine, arginine and N terminus of the proteins where these amino acids react with a reducing sugar such as glyoxal, methylglyoxal etc at the N terminus. The active carbonyl group of the sugar reacts with the nucleophilic free amino group of the protein leading a Schiff's base formation. Amadori products or Ketoamines are formed by a rearrangement in the Schiff base. These Schiff's base further undergoes dehydration and rearrangement, cyclization, oxidation, and dehydration, leading to the formation of a more stable moiety known as glycation end products or advanced glycation end products (AGEs).[17]

2.2. Glycated Hemoglobin

Glycated Hemoglobin or HBA1c is also an AGE and already an established marker for Diabetes and long term glycemic control. The Epidemiology of Diabetes Interventions and Complications study concluded benefits in terms of reduction in risk of advanced diabetes, diabetic eye disease (49%), eye surgery (49%), advanced kidney disease (33%), nerve problems (30%), cardiovascular diseases (such as heart attack and stroke) (30%).[18] Cohen and associates also demonstrated in their seminal work that HbA(1c) (A1C) is substantially determined by genetic factors and is not a direct and accurate determinant of glucose. Heritable Fractional variance in A1C, also called the glycation gap (GG; formerly named as the glycosylation gap) and the hemoglobin glycosylation index, correlate with diabetes complications.[19]

These were significant findings in a longitudinal study of far-reaching significance. It is important to note that Diabetes is not merely implicated directly with the concomitant complications such as Diabetic eye, kidney and nerve disease but the higher amount of AGE's in diabetic population resulting from a higher plasma glucose level are also involved in the various pathological conditions in a causal manner. HbA1c can be measured by a variety of methods in the laboratory and some are Ion Exchange Chromatography, Boronate Affinity Columns and Immunoassays. Each method has its merits, **Table 1** enlists a summary of the merit of each method.

2.3 Comparison of various assay methods for HbA1c

2.3.1.Fructosamine

Fructosamine refers to all glycated serum proteins with ketoamine linkages resulting as a result of glycation in the presence of elevated plasma Glucose levels. Glycated lipoproteins, Glycated Globulins and Serum Albumin form the group of plasma proteins which potentially get glycated of these Serum Albumin is the most abundant. Collectively these are called Fructosamine and are assayed as an Glycation end product. A stable ketoamine of 1-amino-1-deoxy fructose is Fructosamine. In a non-enzymatic manner Glucose reacts with the amino group of protein moieties (predominantly albumin, but also including globulins and lipoprotein), leading to formation of Fructosamine. The aldehyde group of the carbohydrate attaches with the N terminal amino acid of protein forming a Schiff base product or the aldimine intermediate. This is a reversible aldimine or Schiff base and may be converted back to glucose and protein. When this reversible intermediate undergoes Amadori rearrangement to form stable product Fructosamine is formed.[20] This non-enzymatic glycation is also referred to as the Maillard reaction.

A colorimetric-based assay utilizing the reduction of the dye nitroblue tetrazolium (NBT) to formazan is used for measurement of Fructosamine in the blood.[21] Using spectrophotometric methods the rate of formazan formation is measured. This rate is directly proportional to the fructosamine concentration. The reference range for fructosamine in non-diabetic individuals is generally 200 to 285 µmol/L. Malmstrom H[22] and associates demonstrated the usefulness of Fructosamine in distinguishing between diabetics and non-diabetics, by demonstrating the correlation between hbA1c, Glucose in a controlled study. Fructosamine has been associated with cardiovascular disease mortality and morbidity in haemodialysis patients.[23] In a prospective longitudinal 24-year study, no correlation was found between a baseline Fructosamine level and cardiovascular diseas (CVD) event, fatal CHD (coronary heart disease), and all-cause mortality. Cohen and associates performed a study comparing the fructosamine, HbA1c and average glucose values with an objective of finding relevance from the perspective of personalized medicine. A gap between the actual HbA1c value and the predicted value from Furctosamine levels defines the Glycosylation Gap. In the study performed on 153 people a Glycosylation Gap range of -3.2% to 5.5% was found. It was concluded that a mere 1% increase in GG was associated with a significantly high 2.9-fold increase in the risk of nephropathy.[24]

2.5 Glycated albumin

Human Serum Albumin is a 66.5 KDa protein consisting of around 585 amino acids residues organized. The amino acids are organized in a single polypeptide chain with 3 homologous domains (I, II, and III) assembled in a heart-shaped molecule. This structure is stabilized by 17 disulphide bridges. All the three domains are further organized into 2 subdomains namely A and B, with analogous structural motifs. It may not be wrong to say that since Glycated Albumin is the largest constituent of Fructosamine and hence largest of all the AGE's present in blood.[25] Albumin is the largest fraction of serum proteins and serves to maintain the osmotic potential of blood. It is also a constituent of the transport mechanisms being a part of lipoproteins. Many essential biological nutrients bind Albumin. Several conditions impact the homeostasis of Albumin. The balance between albumin production and the total amount of albumin removed by the renal (Re), gastrointestinal (GI), and catabolic (C) processes determines the plasma clearance Cp.[26]

Synthesis = GI loss + Renal loss + catabolism

Glycated Albumin has multiple sites of glycation compared to HbA1c hence the glycation rate of Albumin is approximately 4.5 times faster.[27] It has been reported that for every percentage unit increase in the levels of HbA1c in the erythrocytes there is nearly 3 percentage unit increase in Glycated Albumin.[28] This points to its promise of being a much more sensitive marker of glycation and glycemic control. Glycated albumin Provides valuable insights in conditions of oxidative stress and can act as a biomarker.[29] along with the assessment of beta-cell secretory dysfunction,[30] as well as Glycated Albumin is also

remarkably shown to predict prognosis of diabetic complications and associated comorbidities[31,32] A study conducted in Taiwan compared the screening methods for Diabetes Mellitus using Glycated Albumin and HbA1c. The results showed that mean GA values were 31.2% higher in diabetic subjects and 18.1% higher in controls, while mean HbA1c values were 29.2% higher in diabetic subjects and 5.6% higher in controls. According to the study, the 75th percentile of the normal population would have cut-points for HbA1c and Glycated Albumin for prediabetes of 14.6% and 5.8%, respectively. A 16.5% glycated albumin value is indicative of diabetes, as is a HbA1c level of 6.5%.[33]. For practical purposes Biochemical assays for Glycated Albumin are easier to standardize and automate for larger clinical deployment compared to Fructosamine assay. Additionally, these also suffer from less variability and hence add to their reliability.

2.6 Challenges with HbA1c testing

While HbA1c testing is accepted as a biomarker for long term glycemic control there exist certain challenges in the quantification of HbA1c. One part of the challenges are interference from various types of Hemoglobin traits such as HbC, HbS, HbE, HbD, Elevated HbF, Carbamoylated Hb in different assay methodologies. These factors are difficult to clinically assess and normalize in routine diabetes management both for the diabetic patient and the caregiver. The possibility of cross-reactions with chemically modified hemoglobin species or hemoglobin variants identified by genetics always exists. The glycohemoglobin levels of patients heterozygous for a variant hemoglobin, such as hemoglobin S, C, E, and rarer variations, may therefore be mistakenly raised or lowered.[34] In people of African, Mediterranean and South East Asian descent there exists a higher incidence hemoglobin variant. The heterozygotes may remain undiagnosed and asymptomatic until very late.35 (35). All conditions when HbA1c testing is inadequate and unreliable.[36] Although this is challenge is being addressed by various quality circles, laboratory quality management practices, harmonization initiatives and assay developers the other bigger challenge is more physiological.[36] There are conditions wherein HbA1c may not be the ideal biomarker that it is made out to be.[37,38]. Simplistically put since Hemoglobin is present in Erythrocytes so the increase or decrease in the life of the Erythrocyte will lead to a change in the value of HbA1c which may not correlate clinically.[39]In both conditions either the value would be falsely elevated or falsely low leading to incorrect assessment and corrective actions predisposing the diabetic patient to risks.[40] Some such commonly encountered risks are enumerated below.

1. Iron deficiency Anemias: Treatment leads to lowering of HbA1c.[41,42]
2. Commonly encountered Vitamin B12 and Folate deficiency leads to decreased red cell turnover leading falsely elevated HbA1c values.[39,43]
3. Alcoholism: Several studies have shown that alcoholism leads to elevated HbA1c.[44]
4. Pregnancy: Reduced Erythrocyte lifespan may lead to falsely lower values of HbA1c. Besides this Gestational Diabetes commonly encountered may not be accurately diagnosed using HbA1c as a marker.
5. Anemia from Hemolytic causes will lead to falsely lower HbA1c values.
6. Hepatic disorders leading to Hyperbilirubinemia will lead to falsely elevated HbA1c values.

2.7 Potential role for glycated albumin as a biomarker for diabetes management

Glycated Albumin has a potential role in the management of non-insulin dependent type 2 Diabetes where HbA1c has limitations and together with HbA1c can help in providing a clearer and more accurate status of intermediate glycemic control. Glycated Albumin testing has certain advantages in the family of glycated proteins that result due to elevated plasma Glucose levels.[45]

There may be a need for more research on the use of glycated albumin in the diagnosis and surveillance of diabetes in some populations, particularly in regions like India where iron deficiency anemia is common, particularly in females. As glycated albumin is unaffected by erythrocyte turnover, it likewise exhibits less fluctuation in Chronic Kidney Disease.[46]

When detecting pre-diabetes, glycated albumin testing is more sensitive and specific than HbA1c and fasting blood glucose alone.[47] The combined use of HbA1c and GA demonstrated a higher sensitivity (78%) compared to using HbA1c alone (50%), effectively identifying nearly 80% of African prediabetics. Additionally, a GA level of 17.1% or higher could detect most undiagnosed diabetics. When fasting glucose was measured alongside GA, the rate of false positives was reduced by 33.75% compared to using fasting glucose alone.[48]

3. Discussion

The global prevalence of diabetes is on the rise, necessitating a reevaluation of current diagnostic strategies and the exploration of innovative markers for early detection and intervention. While traditional markers like Fasting Plasma Glucose (FPG) and Hemoglobin A1c (HbA1c) have been key to diabetes management, the increasing number of diabetics worldwide poses challenges that demand a more personalized approach. The intricate connections between diabetes, insulin resistance, and cardiometabolic complications have been extensively researched, underscoring the need for a paradigm shift in diagnostic algorithms.[49]. This article examines the potential of Glycated Albumin as a versatile biomarker and argues for its inclusion in routine diagnostic algorithms. Challenges in Current Diagnostic Approaches: (a) No One Size Fits All: The heterogeneous nature of diabetes

necessitates a reevaluation of current diagnostic algorithms, which often rely on standardized approaches. Recognizing the absence of a one-size-fits-all solution, there is a pressing need to expand criteria by incorporating additional parameters and biomarkers. The complexity of diabetes demands a more personalized diagnostic approach to cater to the diverse nature of the disease. (b) Catching Them Young: Early intervention is crucial in mitigating complications associated with diabetes. Prediabetic screening becomes paramount in preventing a surge in cardiometabolic syndrome-related complications. Identifying individuals in the prediabetic stage provides an opportunity to implement preventive measures, slowing down the progression toward severe complications such as Diabetic Retinopathy, Diabetic Kidney Disease, and Diabetic Foot. The Glycated Albumin's Potential in Diabetes Management: (a) Complementary Role with Traditional Markers: Glycated Albumin emerges as a valuable addition to traditional markers like HbA1c and FPG. In cases where HbA1c alone may not provide accurate information, the combination of Glycated Albumin with HbA1c and FPG enhances sensitivity and specificity. This synergy ensures a more comprehensive understanding of the patient's glycemic status. (b) Marker of Intermediate Glycemic Control: Beyond its role as a diagnostic marker, Glycated Albumin proves to be a marker of intermediate glycemic control. This aspect is particularly beneficial in managing diabetes in patients with associated factors, offering healthcare professionals a more holistic perspective for tailored treatment plans.[50] (c) Sensitive Marker of Prediabetes: Glycated Albumin exhibits higher sensitivity and specificity, along with a faster rate of glycation compared to HbA1c. Its standardized nature positions it as an additional and sensitive marker for identifying individuals in the prediabetic stage. Early detection enables timely interventions, potentially preventing the progression to full-blown diabetes. (d) Automation and Analytical Reproducibility: Glycated Albumin assays, in contrast to alternatives like Fructosamine, are more amenable to automation and offer higher analytical reproducibility and accuracy. This not only streamlines the diagnostic process but also ensures consistent and reliable results, crucial in clinical decision-making.

Like with all clinical tools there are certain limitations with the application of Glycated Albumin. GA levels may also be impacted by certain circumstances that disrupt albumin metabolism. Although low amounts of this protein are linked to higher glycation rates, GA is theoretically unaffected by serum albumin levels because its values are adjusted for total albumin. Conversely, reduced GA levels are linked to higher protein metabolism.[51] Therefore, the administration of GA may be misleading and should be avoided in situations such as nephrotic syndrome with extensive proteinuria, liver cirrhosis, hyperthyroidism, hypothyroidism, or other particular disorders.[52]. However, few studies have been conducted to confirminterferingfactors in GA levels because this test is relatively new. The shorter time to glycation and faster turnover also necessitates more frequent testing for Glycated Albumin levels in a clinical setting. While this is not a bad aspect it will impact patient compliance and costs of management over time.

The evolving challenges in diabetes management necessitate a departure from traditional diagnostic approaches. As we strive to address the variabilities within the diabetic spectrum, Glycated Albumin emerges as a versatile biomarker offering enhanced sensitivity, specificity, and applicability in diverse clinical scenarios. The inclusion of Glycated Albumin in routine diagnostic algorithms becomes imperative for a more personalized and effective diabetes management strategy. In embracing this innovative marker, healthcare professionals can usher in a new consensus for responding to the ever-increasing challenges of diabetes. By recognizing the potential of Glycated Albumin, we move toward a more comprehensive and tailored approach to diabetes diagnosis and management, with the ultimate goal of curbing the global burden of diabetes and its associated complications.

4. Conclusion

Glycated Albumin emerges as a promising marker for short-term glycemic control, offering a unique perspective complementary to HbA1c. In a span of 2-3 weeks, it provides a real-time snapshot of glycemic fluctuations, filling a crucial gap where HbA1c's long-term perspective may be less responsive to recent changes. This temporal specificity proves invaluable in situations demanding immediate adjustments to treatment plans or lifestyle modifications. The synergy between Glycated Albumin and HbA1c extends beyond glycemic control, as together, they serve as predictive indicators of oxidative stress in diabetes. Glycated Albumin's faster rate of glycation makes it a dynamic marker, closely reflecting ongoing stress and consequently, offering insights into the level of oxidative stress. In conditions where HbA1c may be less reliable, such as in instances of altered erythrocyte turnover, Glycated Albumin stands out as a dependable alternative, enhancing our ability to monitor and manage glycemic control effectively. This dual role positions Glycated Albumin as a valuable addition to diabetes diagnostics, promising improved precision and responsiveness in the ever-evolving landscape of diabetes care.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Cohen RM, LeCaire TJ, Lindsell CJ, Smith EP, D'Alessio DJ. Relationship of Prospective GHb to Glycated Serum Proteins in Incident Diabetic Retinopathy. *Diab Care*. 2008;31:(1),151–3.
2. Belinda R. Gale Encyclopaedia of Alternative Medicine. In: Gale Encyclopedia of Alternative Medicine. 2004. p. 2603–5.
3. Nathan DM, McGee P, Steffes MW, Lachin JM. Relationship of Glycated Albumin to Blood Glucose and HbA1c Values and to Retinopathy, Nephropathy, and Cardiovascular Outcomes in the DCCT/EDIC Study. *Diabetes.* 2014;63(1):282–90.
4. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. *Indian J Ophthalmol*. 2021;69(11):2932–8.
5. WHO. https://www.who.int/india/health-topics/mobile-technology-for-preventing-ncds. Diabetes in India.
6. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diab Res Clin Pract*. 2014;103(2):137–49.
7. Mohan V, Pradeepa R. The Global Burden of Diabetes and Its Vascular Complications (Chapter 1). In: Kartha CC, Ramachandran S, Pillai RM, editors. Mechanisms of Vascular Defects in Diabetes Mellitus Advances in Biochemistry in Health and Disease. Springer International Publishing; 2017. p. 3–23.
8. Bastaki S. S. Diabetes mellitus and its treatment. *Int J Diab Metab*. 2024;13:(3),111–34.
9. Standards of medical care in diabetes-2011. Diab Care. 2011;34:(1):11–61.
10. Olokoba AB, Obateru OA, Olokoba LB. Type 2 Diabetes Mellitus: A Review of Current Trends. *Oman Med* J. 2012 Jul;27(4):269-73.
11. Cho S, Duong VA, Mok JH, Joo M, Park JM, Lee H. Enrichment and analysis of glycated proteins. *Rev Anal Chem*; 2022. 41(1): p. 83–97.
12. Forbes JM, Cooper ME. Mechanisms of Diabetic Complications. *Physiol Rev*. 2013 Jan;93(1):137–88.
13. Piero MN. Diabetes mellitus – a devastating metabolic disorder. *Asian J Biomed Pharma Sci*. 2015; 4(40):1–7.
14. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001;414(6865):813–20.
15. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced Glycation End Products. *Circulation*. 2006 Aug 8;114(6):597–605.
16. Vlassara H. Advanced Glycation End-products and Atherosclerosis. *Ann Med.* 1996; ;28:(5)419–26.
17. Kim CS, Park S, Kim J. The role of glycation in the pathogenesis of aging and its prevention through herbal products and physical exercise. *J Exerc Nutr Biochem.* 2017;21(3):55–61.
18. Selvin E, Francis LMA, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, et al. Nontraditional Markers of Glycemia. *Diab Care.* 2011;34(4):960–7.
19. Cohen RM, Snieder H, Lindsell CJ, Beyan H, Hawa MI, Blinko S, et al. Evidence for Independent Heritability of the Glycation Gap (Glycosylation Gap) Fraction of HbA1c in Nondiabetic Twins. *Diab Care.* 2006;29:(8),1739–43.
20. Gillery P. Dosage de l'HbA1c et des produits d'Amadori en biologie humaine. *Ann Pharm Fr*. 2014;72:(5),330–6.
21. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. *Clin Chim Acta.* 1982, 127;(1)87–95.
22. Malmström H, Walldius G, Grill V, Jungner I, Gudbjörnsdottir S, Hammar N. Fructosamine Is a Useful Indicator of Hyperglycaemia and Glucose Control in Clinical and Epidemiological Studies – Cross-Sectional and Longitudinal Experience from the AMORIS Cohort. *PLoS One*. 2014:(10):e111463.
23. Shafi T, Sozio SM, Plantinga LC, Jaar BG, Kim ET, Parekh RS, et al. Serum Fructosamine and Glycated Albumin and Risk of Mortality and Clinical Outcomes in Hemodialysis Patients. *Diab Care*. 2013;36:(6),1522–33.
24. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance Between HbA1c and Fructosamine. *Diab Care*. 2003;26(1):163–7.
25. Roohk HV, Zaidi AR. A Review of Glycated Albumin as an Intermediate Glycation Index for Controlling Diabetes. *J Diab Sci Technol*. 2000;2(6):1114–21.
26. Levitt DG, Levitt MD. Human serum albumin homeostasis: A new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. *Int J Gen Med.* 2016;9(2):229–55.
27. Iberg N, Flückiger R. Nonenzymatic glycosylation of albumin in vivo. Identification of multiple glycosylated sites. *J Biol Chem.* 1986;261(29):13542–5.
28. Ueda Y, Matsumoto H. Recent topics in chemical and clinical research on glycated albumin. In: *J Diab Sci Tech.* 2015;177–82.
29. Selvin E, Francis LM, Ballantyne CM. Nontraditional markers of glycaemia: associations with microvascular conditions. *Diab Care*. 2011;34(4):960–7.
30. Kim D, Kim KJ, Huh JH et al. The ratio of glycated albumin to glycated haemoglobin correlates with insulin secretory function. *Clin Endocrinol*. 2012;77(5):679–83.
31. Sato Y, Nagao M, Asai A. Association of glycated albumin with the presence of carotid plaque in patients with type 2 diabetes. *J Diab Invest*. 2013;4(6):634–9.
32. Furusyo N, Koga T, Ai M et al. Utility of glycated albumin for the diagnosis of diabetes mellitus in a Japanese population study: results from the Kyushu and Okinawa Population Study *Diabetologia*. 2011;54(12):3028–36.
33. Hsu P, Ai M, Kanda E, Yu NC, Chen HL, Chen HW, et al. A comparison of glycated albumin and glycosylated hemoglobin for the screening of diabetes mellitus in Taiwan. *Atherosclerosis*. 2015;242(1):327–33.
34. Little RR, Roberts WL. A review of variant hemoglobins interfering with hemoglobin A1c measurement. *J Diab Sci Tech.* 2009; 3(3):446-51
35. NGSP. http://www.ngsp.org/interf.asp. 2010. HbA1c assay interferences. National Glycohemoglobin Standardization Program Web site.
36. NGSP. NGSP. 2024. Factors that Interfere with HbA1c Test Results. https://ngsp.org/factors.asp
37. Rahma H, Siregar J, Syafril S, Ganie RA, Siregar DIS, Ginting A. Correlation between HbA1c Levels and Red Distribution Cell Width in Type 2 Diabetes Mellitus Patients. *Ind J Med.* 2024 Jan 10;9(1):45–51.
38. Engström G, Smith JG, Persson M, Nilsson PM, Melander O, Hedblad B. Red cell distribution width, haemoglobin <scp>A</scp> 1c and incidence of diabetes mellitus. *J Intern Med*. 2014 Aug 28;276(2):174–83.
39. Arnold JG, McGowan HJ. Delay in Diagnosis of Diabetes Mellitus Due to Inaccurate Use of Hemoglobin A1C Levels. *J Am Board Fam Med*. 2007;20(1):93–6.
40. Panzer S, Kronik G, Lechner K, Bettelheim P, Neumann E, Dudczak R. Glycosylated hemoglobins (GHb): an index of red cell survival. *Blood*. 1982;59(6):1348–50.
41. Brooks AP, Metcalfe J, Day JL, Edwards MS. Iron Deficiency and Glycosylated Hæmoglobin A1. *Lancet.* 1980;316(8186):141.
42. Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediat Int. 1999;41(4):357–62.
43. Joseph Larese. https://www.clinicalcorrelations.org/2012/02/01/when-is-hemoglobin-a1c-inaccurate-in-assessing-glycemic-control/. 2012. When Is Hemoglobin A1c Inaccurate In Assessing Glycemic Control?
44. Hoberman HD, Chiodo SM. Elevation of the hemoglobin A1 fraction in alcoholism. *Alcohol Clin Exp Res*. 1982;6 2:260–6.
45. Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker., *End J.* 2010.57;(9) 751–62.
46. Zelnick LR, Batacchi ZO, Ahmad I, Dighe A, Little RR, Trence DL, et al. Continuous glucose monitoring and use of alternative

markers to assess glycemia in chronic kidney disease. *Diab Care*. 2020;43(10):2379–87.

47. Sumner AE, Duong MT, Aldana PC, Ricks M, Tulloch-Reid MK, Lozier JN. A1C Combined With Glycated Albumin Improves Detection of Prediabetes in Africans: The Africans in America Study. *Diab Care.* 2016;39(2):271–7.
48. He X, Ying L, Ma X, Shen Y, Su H, Peng J, et al. An additional measurement of glycated albumin can help prevent missed diagnosis of diabetes in Chinese population. *Clinica Chimica Acta*. 2017;475:188–92.
49. Fahed G, Aoun L, Zerdan MB, Allam S, Zerdan MB, Bouferraa Y, et al. Metabolic Syndrome: Updates on Pathophysiology and Management. *Int J Mol Sci.* 2021;23;(2)786
50. Zhang J, Zhang Z, Zhang K, Ge X, Sun R, Zhai X. Early detection of type 2 diabetes risk: limitations of current diagnostic criteria. *Front Endocrinol* 2023;14: 1260623
51. Bhonsle HS, Korwar AM, Kote SS, Golegaonkar SB, Chougale AD, Shaik ML, et al. Low Plasma Albumin Levels Are Associated with Increased Plasma Protein Glycation and HbA1c in Diabetes. *J Proteome Res*. 2012;11(2):1391–6.
52. Furusyo N, Hayashi J. Glycated albumin and diabetes mellitus. *Biochim Biophysica Acta (BBA) Ge Sub.* 2013;1830(12):5509–14.
53. Vithian K, Hurel S. Microvascular complications: pathophysiology and management. *Clin Med,* 2010;10(5):505–9.
54. Adeniyi AF, Adeleye JO, Adeniyi CY. Diabetes, sexual dysfunction and therapeutic exercise: a 20 year review. *Curr Diab Rev*. 2011;6(4):201-6.

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