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# Glycated Albumin as a Biomarker for Early Detection of Diabetic Retinopathy: A Narrative Review

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**Abstract** **Background:** Diabetic Retinopathy (DR) is the major cause of vision loss worldwide. Early detection of microvascular damage is crucial for preventing vision loss. The usual marker for long-term glycemia, haemoglobin A1c (HbA1c), has significant drawbacks. Glycated Albumin (GA) measures short-term glycaemic exposure and may detect risk earlier. To summarise current evidence on the role of GA and GA/HbA1c ratio in detecting early DR. **Methods:** A narrative literature review was carried out using Medline (via PubMed), Google Scholar and ScienceDirect. We considered peer-reviewed human studies published in English between 2014 and 2025 that investigated GA, GA/HbA1c ratio, or glycaemic variability in connection to DR. Joanna Briggs Institute critical evaluation tools were used to select studies, retrieve data and assess quality. **Results:** Fifty-nine studies using cross-sectional, case-control and longitudinal cohort designs were included. The studies quality ranged from moderate to good. Numerous studies found a link between higher GA (range from 10 to 16%) levels and DR, regardless of HbA1c. The GA/HbA1c ratio (1.8 to 2.6) and visit-to-visit GA variability were consistently linked with DR risk, indicating that GA captures clinically meaningful glycaemic fluctuations not captured by HbA1c alone. **Conclusion:** Glycated albumin is a promising biomarker for the detection and risk stratification of diabetic retinopathy, particularly in clinical situations where HbA1c may be unreliable or inconsistent. However, the conclusion should emphasize that GA serves as a complementary marker rather than a replacement for HbA1c or retinal imaging.

**Key Words** Glycated Albumin, HbA1c, Diabetic Retinopathy, Biomarker, Glycaemic Variability

## INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic condition in which the body is unable to effectively use insulin, resulting in excessive blood sugar levels. It is a major public health concern around the world, having enormous implications for human life, quality of life and health-care costs [1]. According to estimates from the International Diabetes Federation (IDF), there would be 463 million people with Diabetes Mellitus (DM) worldwide in 2019 and 700 million in 2045 [2]. Diabetes is strongly associated with vascular abnormalities, which can cause tissue and multi-organ dysfunction. These include both macrovascular and microvascular problems. Macroscopic problems include peripheral vascular disease, ischaemic heart disease and cerebrovascular disease, while microvascular complications include neuropathy, retinopathy and nephropathy. Diabetic Retinopathy (DR) is one of the most common microvascular complications of diabetes. Every year, it causes around 10,000 new cases of blindness in the United States alone [3]. Diabetic Retinopathy (DR), which affects over 103 million people worldwide and accounts for 5-10% of all blindness, is still a common result of diabetes mellitus and a major cause of preventable blindness in the working adult population. Its prevalence is predicted to rise due to increasing diabetes incidence, especially in low- and middle-income nations [4]. Early detection and glycaemic control are the main strategies for preventing DR progression. Hemoglobin A1c, the conventional marker of long-term glucose control, reflects mean glycaemia over 8-12 weeks. However, HbA1c can be unreliable in anaemia, haemoglobinopathies, pregnancy, chronic kidney disease and conditions altering red-cell lifespan [5]. Moreover, HbA1c does not capture short-term fluctuations or “glycaemic variability,” which are increasingly linked to microvascular damage [6].

Glycated Albumin (GA) is an amadori ketoamine produced by the non-enzymatic glycation of serum albumin in diabetics. Glycated albumin, an intermediate of advanced glycated end products, accounts for nearly 80% of total glycations in plasma.

Glycated albumin levels rise in the presence of hyperglycemia [7]. It measures glycaemic control during the last three weeks. This feature of GA is used as a measure of glucose management in the blood [8]. In type 2 diabetics, GA is significantly linked with HbA1c and fasting glucose levels. Though measuring HbA1c is the gold standard for monitoring mean glycemia during the last 2-3 months, in cases where HbA1c test may be inaccurate, or quicker clinical decision making is required [9], GA can be a valuable complementary biomarker for assessing blood glucose fluctuations during the last three weeks. Elevated GA levels are significantly associated with diabetic retinopathy [10,11]. It has become a new glycaemic marker at the beginning of the twenty-first century for the diagnosis of diabetes [12]. Glycated albumin reflects short-term glycaemic excursions that promote oxidative stress more strongly than sustained hyperglycaemia alone. Previous studies have shown that glucose fluctuations increase the production of reactive oxygen species, leading to endothelial dysfunction, inflammation and retinal capillary damage, which are key mechanisms in the pathogenesis of DR. As GA is particularly sensitive to postprandial glucose spikes and glycaemic variability, it may serve as a surrogate marker of the metabolic stress that contributes to retinal microvascular injury [13,14]. In Saudi Arabia, the prevalence of DR ranged between 28.1 and 45.7%, with vision-threatening DR affecting 4.5% to 17.5% of diabetic individuals [15]. A meta-analysis of 59 population-based studies found that the global prevalence of DR is 22.27% (95% Confidence Interval (CI), 19.73%-25.03%) [4].

Research in Asian and Western populations has progressively established links between high Glycated Albumin (GA) and the presence or progression of Diabetic Retinopathy (DR) [12,16]. Furthermore, the ratio of GA to HbA1c (GA/HbA1c) and visit-to-visit changes in GA readings have demonstrated potential as independent predictors of DR [14]. Given the high incidence of type 2 Diabetes Mellitus (T2DM) and the significant and growing local burden of DR in Saudi Arabia, GA may have practical utility for enhancing screening and risk-stratification procedures in the Saudi clinical environment [17].

This narrative review aims to examine the current evidence on Glycated Albumin (GA) as a biomarker for early diagnosis of Diabetic Retinopathy (DR) in people with type 2 diabetes. The review assesses GA's merits and limitations, summarizes recent research advancements and investigates its potential relevance in clinical practice. Although several studies have linked GA with DR, recent evidence has expanded to include the GA/HbA1c ratio, GA variability and longitudinal predictors of DR progression. Reviews focusing on the role of GA in early DR detection and risk stratification lacks, highlighting the need for an updated review. Therefore, this narrative review aims to evaluate the current evidence on Glycated Albumin (GA) as a biomarker for the early detection and progression of Diabetic Retinopathy (DR) in patients with type 2 diabetes mellitus. Specifically, it examines the associations of GA, the GA/HbA1c ratio and glycaemic variability with DR and discusses the potential complementary role of GA alongside conventional markers such as HbA1c in clinical risk stratification and screening. This review seeks to help clinicians and researchers improve early detection strategies, guide patient care and inspire future studies on avoiding vision loss in diabetes patients by offering a concise synthesis of new findings.

## METHODS

### Literature Search Strategies and Eligibility

The current review was conducted with adherence to the PRISMA Guidelines.

Before beginning the literature review, a precise search strategy and eligibility framework were developed to guide the inclusion and exclusion of studies. A thorough narrative search was then performed to locate previously published data on Glycated Albumin (GA) and its function in the early identification of Diabetic Retinopathy (DR) in people with type 2 diabetes mellitus. To capture a broad and relevant literature, three main electronic databases were investigated: Medline (via PubMed and Ovid), Google Scholar, ScienceDirect. We considered peer-reviewed human studies published in English between 2014 and 2025 that investigated GA, GA/HbA1c ratio, or glycaemic variability in connection to DR. Joanna Briggs Institute critical evaluation tools were used to select studies, retrieve data and assess quality. The search strategy was developed using a "building blocks" approach combining key conceptual domains: (1) glycated albumin, (2) glycaemic variability / GA-HbA1c ratio and (3) diabetic retinopathy.

Full Boolean search strings used in PubMed included: ("glycated albumin" OR "glycated serum albumin" OR "GA") AND ("diabetic retinopathy" OR "retinal microvascular complications") AND ("type 2 diabetes mellitus" OR "T2DM") AND ("HbA1c" OR "glycaemic variability" OR "postprandial glucose").

Additional searches used combinations of: "GA/HbA1c ratio" "glycated albumin variability" "early detection diabetic retinopathy biomarkers". Searches were limited to peer-reviewed English-language studies published between 2014 and 2025.

Eligibility criteria included observational studies (cross-sectional, case-control, cohort studies) and excluded review articles, editorials, conference abstracts without full data and studies not reporting GA or DR outcomes. Detailed inclusion and exclusion criteria are presented in Table 1. To ensure current and scientifically relevant evidence, the search was restricted to peer-reviewed publications published between 2014 and 2025.

### Article Selection

After doing the literature search, all obtained articles were imported into Mendeley (version 2.110.0; 2024, Elsevier Ltd., London) for reference management. Duplication records were found and eliminated using the software's built-in duplication detection function. The selection of relevant studies was done in three stages. In the first and second steps, the principal reviewer reviewed the titles and abstracts, with assistance from two colleagues familiar with the research area.

Table 1: Inclusion and Exclusion

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Studies examining Glycated Albumin (GA) and its association with Diabetic Retinopathy (DR) | Studies not assessing GA in relation to DR |
| Original research articles (observational studies, diagnostic accuracy studies, clinical trials) | Duplicates |
| Published in peer-reviewed journals | Gray literature such as technical reports, blogs, news articles, conference abstracts, and policy documents |
| Articles published in English | Letters to the editor, opinion pieces, commentaries, book chapters |
| Human studies involving patients with type 2 Diabetes Mellitus (T2DM) | Studies on animals, in vitro studies, or populations other than T2DM |
| Studies reporting outcomes related to GA, GA/HbA1c ratio, glycaemic variability, or early DR | Studies lacking full-text availability |
| Published between 2014 and 2025 | Articles not published in English |

Table 2: Methodological Quality Assessment of Included Studies Using JBI Checklists

| Study Design | No. of Studies (n) | JBI Tool Used | Quality Rating Criteria | Quality Outcome |
|---|---|---|---|---|
| Cross-sectional studies | 34 | JBI Analytical Cross-Sectional Checklist (8 items) | <2 unmet = Strong; 2–3 unmet = Moderate; >3 unmet = Weak | Strong: 18; Moderate: 13; Weak: 3 |
| Cohort/longitudinal studies | 17 | JBI Cohort Checklist (11 items) | Same criteria applied proportionally | Strong: 9; Moderate: 6; Weak: 2 |
| Case-control studies | 6 | JBI Case-Control Checklist (10 items) | Same criteria applied | Strong: 4; Moderate: 2 |
| Mixed-methods/qualitative components | 2 | JBI Qualitative Checklist (10 items) | Narrative quality judgment | Moderate quality |

Studies that did not correspond with the review's objectives were omitted at this stage. In the third stage, full-text articles were thoroughly reviewed to assess eligibility.

### Data Extraction and Quality Assessment

The primary review reviewed all identified papers' titles and abstracts, extracting data relevant to the role of glycated albumin in the early diagnosis of diabetic retinopathy. The methodological quality of the listed studies was evaluated using relevant Joanna Briggs Institute (JBI) critical assessment methodologies. Given that the majority of research in this field are observational or cross-sectional, the JBI checklist for analytical cross-sectional studies (8-item checklist) was predominantly employed, with the checklist for qualitative studies (10-item checklist). The JBI Checklist for Cohort Studies (11-item checklist) was utilised in cohort studies as needed.

Each study was graded for methodological suitability, with quality categorized as strong (<2 criteria unmet), moderate (2-3 criteria unmet), or weak (>3 criteria unmet) (Table 2).

## RESULTS

### Identification of Studies

The initial search of three main databases-Google Scholar, PubMed and ScienceDirect-uncovered a total of 3,728 publications (Google Scholar: 3,320; PubMed: 7, ScienceDirect: 401) published between 2014 and 2025. After eliminating duplicates, 3,412 articles remained for title and abstract screening. During this step, 3,256 articles were discarded because they did not meet the predefined inclusion criteria or had no connection to glycated albumin or diabetic retinopathy (Figure 1). A total of 156 full-text publications were then retrieved for further analysis. Following full-text screening, 97 papers were removed because they largely addressed diabetes management, DR treatment modalities, imaging techniques, or did not report glycated albumin outcomes. Finally, 59 studies met the inclusion criteria and were included in the narrative review. The review included a mix of cross-sectional studies, case-control studies, retrospective and prospective cohort studies from various geographic regions, including East Asia, the Middle East, Europe and North America. This research examined how glycated albumin, GA/HbA1c ratio and glycaemic variability affect the presence, severity and progression of diabetic retinopathy in persons with type 2 diabetes mellitus. The majority of 59 research found a link between higher glycated albumin levels, increased GA/HbA1c ratio, or greater GA fluctuation with the presence or progression of diabetic retinopathy. Table 3 summarises the key characteristics and conclusions from representative studies evaluating GA and DR.

### Association between GA and Prevalent Diabetic Retinopathy

Several cross-sectional research studies have found a significant association between serum GA levels and the occurrence of DR. For example, Korean research of 424 patients with T2DM discovered that people in the highest category of GA had a considerably higher risk of DR than those in the lowest category. This connection remained robust even in patients with mild HbA1c (<8%), demonstrating GA's independent prognostic significance [16].

Umayahara *et al.* [18] studied the GA/HbA1c ratio in relation to microvascular conditions and discovered that a higher GA/HbA1c ratio was associated with DR, showing that GA relative to HbA1c could reflect glycaemic changes relevant to retinal condition.

The GA's association with retinal microvascular disease is supported both clinically and mechanistically by a case-control study by Ijaz *et al.* [19] that demonstrated higher GA % in T2DM patients with DR compared to those without, as well as higher angiopoietin-2 levels in DR cases.

### Predictive Value of GA and DR Progression

The predictive value of GA is supported by longitudinal data. Researchers evaluated HbA1c and GA every three to six months in a retrospective 5-year analysis of 359 people with T2DM; even after controlling for other risk factors, higher mean GA was independently linked to the advancement of DR (OR per unit GA increase = 1.087). This implies that GA might be a more dynamic indicator of risk than just HbA1c [10].

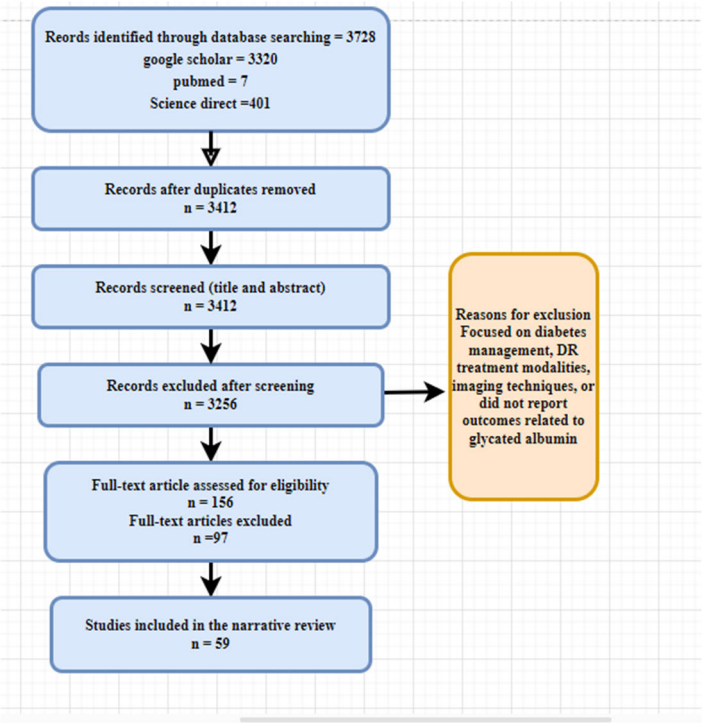


Figure 1: Flow Diagram for the Selection and Identification of Studies for the Narrative Review

Table 3: Summary of Key Studies Evaluating Glycated Albumin and Diabetic Retinopathy

| Author (Year) | Country | Study Design | Sample Size | Population | GA-Related Measure | Main Outcome Related to DR |
|---|---|---|---|---|---|---|
| Jeon *et al.* [16] | South Korea | Cross-sectional | 424 | Adults with T2DM | Serum GA (%) | Higher GA levels were independently associated with prevalent DR, even in patients with HbA1c <8% |
| Umayahara *et al.* [18] | Japan | Cross-sectional | 613 | Adults with T2DM | GA/HbA1c ratio | Elevated GA/HbA1c ratio was significantly associated with DR but not with diabetic nephropathy |
| Ijaz *et al.* [19] | Pakistan | Case-control | 80 | T2DM with and without DR | GA (%) and angiopoietin-2 | GA levels were significantly higher in DR cases; GA correlated with angiopoietin-2, supporting a microvascular mechanism |
| Pan *et al.* [10] | China | Retrospective cohort (5 years) | 359 | Adults with T2DM | Mean GA | Higher mean GA independently predicted DR progression (OR 1.087 per unit increase) |
| ACCORD Eye Study [20] | USA | Randomized trial cohort | >3,000 | Adults with T2DM | GA and glycaemic variability markers | Glycaemic variability measures, including GA, were associated with DR progression beyond HbA1c |
| Zhang *et al.* [21] | China | Cross-sectional | 1571 | Adults with T2DM | GA/HbA1c ratio | GA/HbA1c ratio independently predicted DR after multivariable adjustment |
| Dai *et al.* [14] | China | Observational cohort | 315 | Adults with T2DM | GA variability (CV, VIM, ARV) | Higher visit-to-visit GA variability independently predicted incident DR over 3.4 years |
| Alghamdi *et al.* [23] | Saudi Arabia | Cross-sectional | 428 | Adults with T2DM | HbA1c (risk stratification) | DR prevalence was higher in high-risk glycaemic groups, highlighting need for improved biomarkers |
| Alabdulwahhab *et al.* [24] | Saudi Arabia | Cross-sectional | 327 | Adults with T2DM | HbA1c (risk stratification) | DR prevalence was higher in high-risk glycaemic groups, highlighting need for improved biomarkers |
| Lee *et al.* [27] | Taiwan | Cross-sectional | 291 | Prediabetes (Adults) | The association between glycated albumin, glycohemoglobin, and glycated albumin to glycohemoglobin ratio in diabetic retinopathy | Neither GA nor GA/$HbA_{1c}$ ratio, is significantly associated with DR |
| Saudi Ophthalmology Society | Saudi Arabia | Guideline document | — | T2DM population | — | Guidelines emphasize early DR detection but rely mainly on imaging rather than biochemical markers |

The ACCORD Eye Study found that measures of glycaemic variability, including GA, were associated with DR progression, confirming GA's importance as a dynamic predictor beyond HbA1c [20].

### The GA/HbA1c Ratio as a Marker of Glycemic Fluctuations

The GA/HbA1c ratio has been studied as a measure of glycaemic variability (particularly postprandial spikes). A cross-sectional research of 613 T2DM patients discovered that having a higher GA/HbA1c ratio was substantially linked with DR (independent of other variables), but not with diabetic nephropathy [18].

A recent study published in the International Journal of Clinical Medicine discovered that the GA/HbA1c ratio independently predicted DR, even after accounting for other clinical indicators such as albuminuria [21].

Overall, longitudinal evidence supports GA as a clinically relevant predictor of DR occurrence and development, especially when combined with HbA1c and GA variability [22].

### Visit-to-Visit Variability in Glycated Albumin

In more recent times, prospective research has highlighted that incident DR is predicted by both mean GA and visit-to-visit variability in GA. Even after adjusting for mean HbA1c and other risk variables, higher visit-to-visit GA variability measures (coefficient of variation, VIM and ARV) were independently linked to a higher chance of developing DR in a prospective cohort study (n = 315; mean follow-up ≈3.4 years) [14].

### Clinical and Regional Relevance to Saudi Arabia

Cross-sectional observational research of 428 T2DM patients in Saudi Arabia revealed that DR was more common in high-risk individuals (based on HbA1c ≥9%) than in low-risk patients (HbA1c ≤7%), underscoring the local burden and the need for improved risk classification [23]. Another cross-sectional observational research of 327 T2DM patients in Saudi Arabia revealed similar results and recommendation [24]. Furthermore, early detection of retinal condition is emphasised in Saudi guidelines for Diabetic Macular Oedema (DME), although they now rely more on imaging than biochemical diagnostics [25].

## DISCUSSION

This narrative review shows the recent data supporting Glycated Albumin (GA) as complementing biomarkers for early identification and progression of diabetic retinopathy. Several cross sectional and longitudinal studies have linked higher GA levels to DR and its progression, even after controlling for HbA1c and other risk variables [16,18,26]. Lee and his group found no significant association between GA and DR in their study group [27].

The strength of evidence varies across study designs. Longitudinal cohort studies provide stronger evidence for a temporal association between GA and DR progression, whereas cross-sectional studies primarily demonstrate associations and cannot establish causality. Therefore, findings from prospective studies may be considered more informative for risk prediction than those derived from cross-sectional analyses. From a clinical perspective, GA appears most useful as a complementary biomarker rather than a replacement for HbA1c. Its ability to reflect short-term glycaemic changes and glycaemic variability may improve identification of patients at increased risk of DR, particularly when HbA1c measurements are unreliable. However, variability in assay methods and the lack of standardized cut-off values currently limit widespread clinical implementation.

Importantly conditions that alter serum protein metabolism including liver disease can significantly affect GA levels independently of glycaemia, while nephrotic syndrome and other protein-losing states increase albumin turnover, potentially leading to falsely low GA values. Conversely, dehydration or reduced protein turnover may increase GA independent of glycaemic status. These confounders are not consistently controlled for across studies and may limit the accuracy of GA in complex clinical populations [28,29].

The GA's clinical relevance stems from its capacity to reflect short-term glycaemic control and subsequent glucose deviations, both of which are increasingly recognised as contributing factors to microvascular damage [28,29]. According to experimental and clinical investigations, glycaemic fluctuation enhances oxidative stress, endothelial dysfunction and inflammatory pathways that contribute to retinal microvascular injury [30]. Because serum albumin has a shorter half-life than haemoglobin, GA reacts more quickly to blood glucose changes and may thus detect early metabolic instability associated with DR risk [31].

Recent study evidence suggests that the GA/HbA1c ratio can serve as an indirect indicator of glycaemic variability. Studies from East Asian populations show that a greater GA/HbA1c ratio is independently linked with DR, even in patients with equivalent HbA1c levels [10,18]. Furthermore, longitudinal investigations have indicated that both mean GA levels and GA fluctuation between visits are linked with DR progression, emphasising the importance of dynamic glycaemic exposure rather than static averages alone [26,32].

Glycated albumin should not be viewed as a substitute for ophthalmic assessment but rather as a complementary biomarker that may help identify patients at increased risk who could benefit from earlier or more frequent retinal evaluation [16,26]. Glycated albumin provides fundamentally different clinical information when compared with retinal imaging modalities such as Optical Coherence Tomography (OCT), retinal photography and fundus fluorescein angiography. Because of that retinal imaging remains the gold standard for detecting, grading and monitoring structural retinal changes associated with DR, whereas GA reflects systemic glycaemic exposure and variability [25].

Glycated albumin has several potential barriers that limit its clinical implementation. These include variability in assay methods, lack of universally accepted diagnostic thresholds, limited incorporation into clinical guidelines and differences in laboratory availability across healthcare systems [30,31]. More limitation of GA is its cost-effectiveness compared

with established measures such as HbA1c and retinal imaging, which may hinder widespread adoption in routine practice. Further standardization and prospective validation studies are required before GA can be incorporated into DR screening pathways on a broader scale [26,33,34].

Glycated albumin may be useful for patients with anaemia, hemoglobinopathies, chronic renal illness, or altered red blood cell turnover who cannot rely on HbA1c [35]. This is especially important in low and middle-income nations, as well as places with a high prevalence of diabetes and other comorbidities. In Saudi Arabia and similar settings, where DR prevalence remains significant, GA could supplement existing screening efforts by improving early risk stratification alongside retinal imaging [4,36].

### Strengths

This review includes information from cross sectional and longitudinal research on GA, GA/HbA1c ratio and glycaemic variability in connection to DR. It focus on early detection, which is a major weakness in current DR preventive strategies.

## CONCLUSION

Glycated Albumin (GA) is a promising complementary biomarker for the early diagnosis and progression assessment of Diabetic Retinopathy (DR), as this narrative review shows. Even in those with moderately managed HbA1c, the majority of evaluated studies demonstrate that increased GA is independently linked with DR, underscoring its capacity to capture short-term glycaemic fluctuation. In clinical settings like anaemia or chronic renal disease, when HbA1c is inaccurate, GA may be especially helpful. While the results indicate that GA may be useful in enhancing early screening and risk assessment.

### Limitations

As a narrative review, this work is at risk of selection bias and lacks pooled quantitative estimates. The majority of known research are cross-sectional, making causal inference difficult and GA assay techniques and cut-off values vary significantly [37]. Furthermore, evidence for the use of GA in prediabetes and early Dysglycaemia is lacking. Interpretation of GA may be affected by conditions that alter albumin metabolism or turnover. Liver disease, nephrotic syndrome, thyroid disorders, severe inflammation and protein-losing conditions can influence serum albumin kinetics and may lead to overestimation or underestimation of glycaemic status when GA is used as a biomarker. These factors should be considered when interpreting GA values in clinical practice. A major limitation of this study is that it was conducted by a single author.

Well-designed prospective studies are required to validate standardized thresholds and to assess whether GA-guided screening or therapies improve visual results.

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