Circulating glycated albumin levels and gestational diabetes mellitus

Xiong W et al. Circulating GA levels and GDM

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BACKGROUND
Gestational diabetes mellitus (GDM) is characterized by glucose intolerance that is first diagnosed during pregnancy, making it the most common complication associated with this period. Early detection and targeted treatment of GDM can minimize foetal exposure to maternal hyperglycaemia and subsequently reduce the associated adverse pregnancy outcomes. Previous studies have inconsistently suggested that the level of glycated albumin (GA) might predict GDM.

AIM
To review and synthesize existing evidence to evaluate the relationship between GA levels and the development of GDM.

METHODS
We sought to compare GA levels between GDM and control groups in this meta-analysis by systematically searching the Web of Science, PubMed, Cochrane Library, and Embase databases for articles published up to June 2023. The analysis utilized the weighted mean difference (WMD) as the primary metric. The data were meticulously extracted, and the quality of the included studies was assessed. Additionally, we conducted a subgroup analysis based on study region and sample size. We assessed heterogeneity using I² statistics and evaluated publication bias through funnel plots. Additionally, trim-and-fill analysis was employed to detect and address any potential publication bias.
RESULTS
The meta-analysis included a total of 11 studies involving 5477 participants, comprising 1900 patients with GDM and 3577 control individuals. The synthesized results revealed a notable correlation between elevated GA levels and increased susceptibility to GDM. The calculated WMD was 0.42, with a 95% confidence interval (95% CI) ranging from 0.11 to 0.74, yielding a P value less than 0.001. Concerning specific GA levels, the mean GA level in the GDM group was 12.6, while for the control group, it was lower, at 11.6. This discrepancy underscores the potential of GA as a biomarker for assessing GDM risk. Moreover, we explored the levels of glycated haemoglobin (HbA1c) in both cohorts. The WMD for HbA1c was 0.19, with a 95% CI ranging from 0.15 to 0.22 and a P value less than 0.001. This observation suggested that both GA and HbA1c levels were elevated in individuals in the GDM group compared to those in the control group.

CONCLUSION
Our meta-analysis revealed a substantial correlation between elevated GA levels and increased GDM risk. Furthermore, our findings revealed elevated levels of HbA1c in GDM patients, emphasizing the significance of monitoring both GA and HbA1c levels for early GDM detection and effective management.

Keywords: Glycated albumin; Gestational diabetes mellitus; Diabetes mellitus; Meta-analysis; Weighted mean difference


Core Tip: The aim of this investigation was to elucidate the relationship between glycated albumin (GA) levels and the development of gestational diabetes mellitus (GDM), a prevalent gestational complication characterized by glucose intolerance. Emphasizing the importance of early diagnosis and intervention, this study used a meta-analytical
approach to consolidate existing evidence, thereby performing a comprehensive examination of GA as a potential biomarker for GDM. By aggregating data from diverse studies, this research not only corroborated the association of elevated GA levels with increased GDM risk but also highlighted the significance of glycated haemoglobin (HbA1c) in this context. Consequently, the findings advocate for the inclusion of GA and HbA1c monitoring in prenatal care practices as a means to enhance early detection and management strategies for GDM, aiming to mitigate the adverse outcomes associated with this condition.

INTRODUCTION

Gestational diabetes mellitus (GDM) involves a range of abnormal glucose metabolism observed in pregnant women. It is defined as hyperglycaemia first diagnosed during pregnancy, typically in the second or third trimester, and is one of the most frequent medical complications associated with pregnancy\(^1\). GDM affects approximately 14.8% of pregnant women in China and is a considerable public health concern\(^2\). Indeed, it has been suggested that one in every six pregnancies worldwide is impacted by GDM\(^3\). The complications associated with GDM are numerous and can affect both the mother and foetus. Foetal complications include macrosomia, shoulder dystocia, newborn asphyxia, neonatal respiratory distress syndrome, neonatal hypoglycaemia, and premature birth. In contrast, maternal complications include preeclampsia, an increased risk of caesarean section, an increased risk of type 2 diabetes later in life, and a twofold increase in the risk of developing hypertension and ischaemic heart disease\(^4\).

Research indicates that effective GDM treatment can decrease the incidence of short-term perinatal complications and enhance maternal quality of life\(^5\). Given these implications, it is crucial to systematically identify at-risk individuals and accurately diagnose GDM\(^6\). Currently, the oral glucose tolerance test (OGTT), conducted between the 24th and 28th weeks of gestation, is the standard diagnostic method for GDM, with universal screening recommended in populations with a high prevalence of type 2 DM (T2DM)\(^7\). However, the OGTT is cumbersome, time-consuming, and necessitates a
fasting state[8], leading to interest in identifying reliable, easily measurable biomarkers that could supersede the traditional OGTT.

Glycated albumin (GA) is a primary precursor of advanced glycation end products and reflects mean glucose levels over the past 2-3 weeks[9]. GA, a specific glycated product of albumin, has emerged as a vital indicator of blood glucose control[10]. Importantly, it is not influenced by serum albumin levels, as it is expressed as a ratio to total serum albumin[11]. Thus far, serum GA has been proposed as a reliable, specific, and sensitive serological diagnostic test and marker to supersede haemoglobin (HbA1c) levels in diabetic patients with chronic kidney disease[12] owing to its independence from anaemia and associated treatments. Furthermore, relative to HbA1c levels, GA levels can more rapidly reflect changes or fluctuations in blood glucose levels, which is particularly advantageous for patients with wide blood glucose variations or those at an elevated risk for hypoglycaemia[13]. However, these benefits have yet to be confirmed in large-scale clinical trials and systematic meta-analyses. Therefore, a contemporary meta-analysis to consolidate these findings is warranted.

Motivated by this context, we performed the present study. Our goal was to explore the relationship between GA levels and GDM risk.

MATERIALS AND METHODS

Search strategy

We searched for articles investigating GA levels in GDM patients and control individuals in electronic databases, including Web of Science, PubMed, the Cochrane Library, and Embase. This search adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency, accuracy, and comprehensiveness in the systematic review process[14]. We aimed to identify articles published up until June 2023. Our search strategy incorporated various combinations of the following medical subject headings: “diabetes, gestational”, “gestational diabetes mellitus”, “pregnancy-induced diabetes”, and “glycated albumin”. In addition to this electronic search, we manually searched the reference lists of selected articles to identify
any further studies potentially eligible for inclusion. The detailed retrieval strategy is presented in Supplementary material (Supplementary File 1).

**Inclusion and exclusion criteria**

To be included in the present meta-analysis, studies had to be observational studies, including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies of women diagnosed with diabetes during pregnancy, with an explicit assessment of GA levels. The exclusion criteria were as follows: (1) Studies including women who were diagnosed with type 1 or 2 diabetes before pregnancy; (2) Laboratory studies, nonhuman research, letters, and review articles; and (3) Studies failing to report the women’s GA levels and/or the incidence of GDM.

According to the selection criteria for our meta-analysis, the control group comprised pregnant women who were confirmed to not have GDM, either by a normal OGTT or by not observing any signs of gestational diabetes during pregnancy. The control individuals were carefully matched with the GDM patients in terms of age, body mass index, and gestational week to minimize potential confounding factors. Furthermore, we excluded studies in which the control subjects had any other form of diabetes or significant medical conditions that could interfere with GA levels.

**Data extraction**

The data were meticulously extracted using a standardized, predetermined data collection form. These data included: (1) Study characteristics (author, year, study design, and country); (2) Study groups (sample size); (3) Methods (GDM screening/diagnostic criteria); and (4) GA levels in GDM patients and control subjects.

**Quality assessment**

The methodological quality of the included studies was assessed utilizing the Newcastle-Ottawa Scale, a validated tool designed to evaluate the quality of nonrandomized studies in meta-analyses. This scale allows for the assessment of a study from three broad
perspectives: The selection of the study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest. A maximum score of 9 points can be achieved, considering selection, comparability, the exposure (for case-control studies), or the outcome (for cohort studies). Studies scoring over 7 points are classified as high-quality studies.

Statistical analysis
Outcomes for continuous variables are expressed as weighted mean differences (WMDs) with 95% confidence intervals (CIs). Heterogeneity was evaluated using $I^2$ values, where values below 25% indicated low heterogeneity, values of 25% to 50% indicated moderate heterogeneity, and values exceeding 50% indicated high heterogeneity. For analyses with an $I^2 > 50\%$, a random-effects model was employed, whereas a fixed-effect model was used for analyses with an $I^2 \leq 50\%$. Subgroup analyses were conducted according to the country where patients were included and sample size. A sensitivity analysis was carried out to explore the robustness and stability of the study findings by excluding low-quality studies. A funnel plot was used to assess potential publication bias, with asymmetry in the plot serving as an indication of bias. All the statistical analyses were conducted using Stata (Stata SE, version 15).

RESULTS

Identification of studies
We identified 1036 studies using our search strategy. After deduplication, we screened titles and abstracts to exclude studies that were not relevant to our analysis. Subsequently, 11 studies were found to meet the inclusion criteria. The flow chart of the study selection process is depicted in Figure 1.

Study characteristics
Adhering to the inclusion and exclusion criteria, a total of 11 articles involving 5477 patients diagnosed with GDM were included in our analysis. Patient characteristics and
other pertinent information extracted from each study are summarized in Table 1. The quality assessment results indicated moderate quality across all 11 studies, as shown in Table 1. Notably, of the 11 studies selected, 5 were conducted in China. The measurement of GA in patients with GDM was primarily conducted between 24 and 28 weeks of gestation. There was only one study\textsuperscript{27} that deviated from this range, where the GA levels were measured at 36-38 weeks of gestation. All included studies evaluated GA levels using standardized and internationally approved laboratory methodologies, specifically enzyme-linked immunosorbent assay (ELISA). One study reported the GA level in mmol/mL, while the others reported the GA level in mmol/mL (%). To address this issue and ensure consistency, we used a unit conversion equation. The conversion equation we used was GA (%) = 0.05652 \times \text{GA (mmol/mol)} - 0.4217\textsuperscript{28}. This equation enabled us to standardize the GA values into the same unit across all studies.

**Meta-analysis**

We initially carried out an analysis examining the correlation between GA levels and GDM risk across all patients. The pooled WMD for GA levels and GDM risk was 1.03 (95%CI: 0.33-1.74; \(I^2 = 98.1\%, \ P < 0.001\)) (Figure 2A). As the pooled WMD exhibited significant heterogeneity, we proceeded to perform a sensitivity analysis and assessed publication bias using funnel plots (Figure 3A and B). Two studies\textsuperscript{18,21} were identified as the primary sources of heterogeneity. Upon exclusion of these studies, the pooled WMD for GA levels and GDM risk in all patients decreased to 0.42 (95%CI: 0.11-0.74; \(I^2 = 75\%, \ P < 0.001\)) (Figure 2B). We conducted a sensitivity analysis and evaluated publication bias by visually inspecting a funnel plot (Figure 3C and D). The sensitivity analysis confirmed the robustness of this result. The funnel plot displayed asymmetry, suggesting potential publication bias. Therefore, we employed the trim-and-fill method to reassess the pooled prevalence (Figure 4). The trim-and-fill analysis did not alter the summary effect estimate, indicating that publication bias is unlikely to significantly influence the results of our meta-analysis.
We also analysed the expression of glycated HbA1c in the two groups. The results showed that the pooled WMD for GA levels and GDM risk in all patients decreased to 0.19 (95%CI: 0.15-0.22; I² = 31.1%, P < 0.001) (Supplementary Figure 1).

DISCUSSION

This meta-analysis revealed that there is a significant correlation between elevated levels of GA and an increased risk of GDM. The average GA level was notably greater in the GDM group, underscoring the potential of GA as a predictive biomarker for GDM.

GA has advantages over HbA1c as a biomarker. First, because the half-life of albumin is approximately 2-3 weeks, GA increases in response to hyperglycaemia and thereby represents the mean glucose level over a similar period\(^{[29]}\). Consequently, multiple clinical studies have underscored GA as a more effective indicator of short-term glycaemic variability than HbA1c. Second, GA is unaffected by iron metabolism. In the later stages of pregnancy, iron deficiency anaemia often arises due to increased iron demand, which elevates HbA1c levels relative to the actual glycaemic state. As GA is not correlated with HbA1c, it remains uninfluenced by iron deficiency anaemia\(^{[30]}\). This study included several patients whose HbA1c levels were high but whose GA levels fell within normal ranges.

GA, similar to HbA1c, is strongly correlated with diabetic complications and even mortality in individuals with diabetes\(^{[31]}\). GA levels are independent of the serum albumin concentration, and fasting is not required for GA detection\(^{[32]}\). A recent study exploring the value of measuring GA in GDM patients reported that GA was less influenced by insulin resistance and diastolic blood pressure than was HbA1c. The authors proposed that GA might be superior to HbA1c for monitoring women with GDM\(^{[33]}\). Serum GA levels change swiftly in response to glucose fluctuations. Increased blood glucose levels hinder absorption from kidney tubules by competing with 1,5-AG.

Although our meta-analysis highlights the potential of GA as a predictive biomarker for GDM, we acknowledge that our results did not directly compare GA with traditional markers such as HbA1c and fasting plasma glucose (FPG). Numerous studies have
shown that HbA1c levels reflect long-term glucose control, while GA levels might be more sensitive to short-term fluctuations in blood glucose levels[33-34]. Therefore, GA might offer a timelier indication of glycaemic status, which could be particularly useful in the dynamic physiological context of pregnancy. In terms of predicting GDM, some studies have found GA to be superior to HbA1c[22,23], while others have their predictive abilities to be similar[16,17]. We acknowledge that the relative performance of GA and HbA1c may depend on various factors, such as the timing of measurement and the specific population under study. However, the ability of GA to detect and predict GDM compared to that of FPG still needs further exploration. Some studies suggest that GA may be more sensitive than FPG in detecting early glucose intolerance due to its reflection of short-term glucose fluctuations, but more research is needed to fully understand this relationship. In conclusion, our study indicates the potential role of GA in predicting GDM, but further research is needed to compare its effectiveness and reliability with those of traditional biomarkers such as HbA1c and FPG.

In our study, we focused on the association between GA levels and GDM risk, whereas another published meta-analysis investigated the role of GA in predicting mortality risk in dialysis patients with DM. Although both meta-analyses involved GA as a key factor, the population and clinical outcomes examined in each study were distinct. Previous meta-analyses have also explored the role of GA in diabetic patients, particularly in predicting various clinical outcomes such as all-cause mortality, cardiovascular mortality, and cardiovascular events[34]. These studies have provided valuable insights into the role of GA as a potential biomarker in diabetic patients, particularly for those undergoing dialysis. However, our study specifically targeted pregnant women and the development of GDM, which is a separate clinical context with unique challenges and implications. It is important to acknowledge and discuss the literature on GA levels in diabetic patients, as it helps to contextualize our findings and contributes to a broader understanding of the potential role of GA as a biomarker in different patient populations. Although the results of the published meta-analysis on dialysis patients with DM suggest that GA may predict all-cause mortality risk, our study aimed to assess the association.
between GA levels and the development of GDM in pregnant women. Our findings indicate a possible relationship between higher GA levels and increased GDM risk, but further research is needed to confirm that GA is a potential biomarker for GDM.

The noteworthy correlation found in our meta-analysis between elevated GA levels and increased GDM risk offers valuable insights for clinicians in the identification and management of GDM. By utilizing GA as a potential biomarker in conjunction with existing diagnostic methods, health care professionals may be able to enhance the accuracy and efficiency of GDM detection and intervention. In clinical practice, accurately determining cut-off values is crucial for the appropriate application of biomarkers. Further research is warranted to establish optimal GA cut-off values for GDM prediction, considering factors such as population characteristics, ethnic backgrounds, and methodological variations in GA measurements. Establishing accurate cut-off values may contribute to improved clinical decision-making and targeted GDM management strategies, ultimately improving maternal and foetal health outcomes. It is important to emphasize that integrating the measurement of GA into clinical practice should be approached with caution until additional research provides more substantial evidence for its reliability and validity as a biomarker. Future studies should also address potential confounding factors and methodological issues that might influence the performance of GA in GDM prediction, ensuring its utility in diverse clinical settings. By building upon our findings and addressing these concerns, the scientific community can contribute to optimizing GDM identification and management and enhancing health care outcomes for both mothers and their offspring.

However, some inherent limitations of the study warrant consideration. First, several included studies had relatively small patient populations, limiting the strength of the conclusions drawn due to the limited data on the relationship between GA levels and GDM risk. The small patient numbers and ethnic variation are primarily responsible for the wide confidence intervals. Second, this meta-analysis relied on evidence from observational studies and was limited to English-language publications due to potential mistranslation issues. The absence of randomized controlled trials directly comparing the
prognostic efficacy of GA with that of other glycaemic markers, alongside the inclusion of observational and cross-sectional studies, limited this analysis. Another confounding factor is the study population characteristics, as most studies in this meta-analysis were conducted in China. It remains uncertain whether these findings are applicable to European nations, given the substantial variations in dietary habits, cultural factors, comorbidities (such as metabolic syndrome or obesity), ethnicity, and genetic diversity in European countries compared to Asian countries. Third, there is no unified standard cut-off value. Although our results indicate that high GA values predict a greater GDM risk, the optimal cut-off value for prognosis prediction remains undetermined.

CONCLUSION

In conclusion, our findings revealed a significant association between GA levels and GDM risk. GA offers considerable potential for early risk assessment and informed treatment decisions, which could profoundly influence resource allocation, health care expenditures, and patient outcomes. Further research is warranted to investigate the role of GA in risk stratification among GDM patients.

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Figure 1 Flow of study selection.

Figure 2 Forest plot evaluating glycated albumin levels in people with gestational diabetes mellitus versus those without gestational diabetes mellitus. A and B: The pooled results are expressed as weighted mean differences with 95% confidence interval. 95%CI: 95% confidence interval; WMD: Weighted mean differences.

Figure 3 Sensitivity analysis and funnel plots for publication bias. A: Sensitivity analysis for the effects of glycated albumin levels on gestational diabetes mellitus risk; B: Publication bias analysis based on a funnel plot; C: Sensitivity analysis for the effects of glycated albumin levels on gestational diabetes mellitus risk; D: Publication bias analysis based on a funnel plot. WMD: Weighted mean differences.

Figure 4 Trim-and-fill analysis of the studies included.
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GDM: Gestational diabetes mellitus; NOS: Newcastle-Ottawa Scale.
### ORIGINALITY REPORT

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