

1,5-Anhydroglucitol: From Short-Term Glycemic Monitoring to Risk Stratification of Diabetes Complications

Huijuan Xu^{1,2}, Qiwei Tang^{1,2}, Qiu Chen¹

¹Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People's Republic of China;

²School of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People's Republic of China

Correspondence: Qiu Chen, Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, No. 39 Shi-er-qiao Road, Chengdu, Sichuan, 610072, People's Republic of China, Email chenqiu1969@163.com

Abstract: 1,5-anhydroglucitol (1,5-AG) is sensitive and rapid to glycemic fluctuations. It is important for short-term glycemic monitoring, as it can reflect the glycemic fluctuations within the last 1–2 weeks, as well as postprandial hyperglycemia. Numerous studies have demonstrated that 1,5-AG is associated with diabetic nephropathy, diabetic retinopathy, diabetic cardiovascular diseases, diabetic cerebrovascular diseases, diabetic neurodegeneration, and diabetic pregnancy complications. Therefore, 1,5-AG has potential application value in the risk stratification of diabetes complications and can serve as a complementary biomarker for the risk assessment of diabetes complications. Salivary 1,5-AG, as a non-invasive indicator for glycemic monitoring, is well accepted by patients with remarkable advantages in compliance and shows promising clinical application prospects. However, the relevant detection methods still need to be optimized and improved. This review summarizes the basic characteristics of 1,5-AG and systematically elaborates its clinical application value and research status in diabetes complications, aiming to provide a reference for the rational clinical application and future research of 1,5-AG.

Keywords: diabetes, glycemic control, complementary biomarker, assessment

Introduction

The prevalence of diabetes has been increasing in recent years, and a recent report by the International Diabetes Federation¹ shows that nearly 500 million people worldwide suffer from diabetes. The prevalence rate will continue to rise over time, with an expected 51% increase by 2045. Diabetes is a chronic disease caused mostly by absolute or relative deficiency of insulin secretion or insulin action disorders, with hyperglycemia as the main clinical feature.² Patients with poor long-term glycemic control are more likely to develop complications, which in turn affect the functions of major target organs such as the heart, brain, and kidneys, as well as their prognosis. Moreover, delayed complication diagnosis exacerbates disease progression, increases hospitalization rates, and raises the costs of critical care and long-term rehabilitation. It is the major cause of morbidity and mortality, reducing patients' quality of life³ and significantly increasing medical expenses. Meanwhile, complications such as diabetic foot resulting in ambulatory dysfunction and diabetic retinopathy causing visual impairment lead to reduced labor capacity and an increased family care burden. Thus, delayed complication diagnosis not only increases direct medical expenditure but also adds to indirect social costs, thereby imposing a severe economic burden. Therefore, early assessment of the risk of diabetic complications allows us to implement appropriate interventions to slow disease progression, which is of vital clinical value and public health significance for improving patient prognosis and reducing the economic burden on families and society.

Traditional indicators such as fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and oral glucose tolerance test (OGTT) can be used for diabetes management⁴ and assessing the risk of developing diabetes complications.⁵ However, FPG fails to identify patients with isolated postprandial hyperglycemia, and the test results

are easily influenced by the previous day's dinner and sleep quality. HbA1c cannot promptly and accurately reflect short-term glycemic fluctuations and is affected by the lifespan of red blood cells⁶ and alcohol consumption,⁷ making it difficult to reflect the glycemic control of patients with hemolysis or those who intake alcohol. The operation process of OGTT is relatively cumbersome, requiring patients to undergo multiple blood samplings over a long period of time and strictly control their diet and activities, resulting in poor patient compliance. In conclusion, these traditional glycemic monitoring indicators have their own advantages and disadvantages (Table 1).

With the continuous in-depth research on diabetes, 1,5-anhydroglucitol (1,5-AG) has gradually received widespread attention. A study⁸ showed that 1,5-AG was significantly negatively correlated with FPG and HbA1c. Kappel BA et al⁹ also confirmed that lower levels of 1,5-AG were significantly associated with poor glycemic control through comprehensive metabolomics. 1,5-AG is sensitive and rapid to glycemic fluctuations.¹⁰ It can accurately reflect glycemic fluctuations in the last 1–2 weeks, as well as postprandial hyperglycemia, and can even capture daily blood glucose deviations,¹¹ which can be used for risk stratification of diabetes complications. In addition, salivary 1,5-AG is noninvasive and easy to detect clinically, so there has been a proliferation of related studies.

In recent years, continuous glucose monitoring (CGM) has developed rapidly. Its derived indices, including time in range (TIR), glycemic variability (GV), and mean amplitude of glycemic excursions (MAGE), can accurately reflect short-term glycemic fluctuations and homeostasis. They serve as important evidence for refined glycemic management and also assist in assessing the risk of diabetes complications.^{12–15} However, TIR relies on continuous CGM data collection, is relatively costly, and cannot reflect absolute blood glucose levels. The GV index system is complex and lacks unified standards; it is susceptible to monitoring conditions and shows insufficient stability. MAGE requires professional software for calculation, is cumbersome to operate, and highly depends on CGM data. In addition, CGM requires long-term wearable devices, which impair daily comfort and carry risks such as skin allergy and local infection. Coupled with high testing costs and the complexity of interpreting massive glucose data, CGM is difficult to popularize in primary care settings and large-scale population screening. In contrast, 1,5-AG offers advantages including convenient detection, low cost, the requirement of only a single blood sample, and stable and reliable results. Studies^{16–19} have confirmed that 1,5-AG is positively correlated with TIR and negatively correlated with GV and MAGE. The cutoff value of 1,5-AG for predicting TIR $\geq 70\%$ is 7.8 $\mu\text{g/mL}$. Su H et al²⁰ reported that the performance of 1,5-AG in assessing abnormal carotid intima-media thickness in elderly patients with type 2 diabetes mellitus (T2DM) was comparable to that of TIR, suggesting its potential as a biomarker for subclinical atherosclerosis. 1,5-AG can compensate for HbA1c limits, making it ideal for those with mild glycemic abnormalities, near-target glycemic control, and those unable to use CGM, showing broad application prospects.²¹ Nevertheless, 1,5-AG cannot replace traditional glycemic monitoring indicators

Table 1 The Advantages and Disadvantages of Traditional Glycemic Monitoring Indicators

Traditional Glycemic Monitoring Indicators	Advantages	Disadvantages
Fasting plasma glucose	Convenient, only require a single blood draw on an empty stomach. Reflect the instantaneous blood glucose level quickly. Low cost.	Miss the diagnosis of isolated postprandial hyperglycemia. Affected by the previous day's dinner and the quality of sleep. Cannot reflect the fluctuations in blood glucose.
Glycosylated hemoglobin	Reflect the average blood glucose level over the past 2–3 months. Convenient to detect without the need for fasting. Good stability.	Cannot reflect the immediate blood glucose level. Not sensitive to short-term changes in blood glucose. Affected by the lifespan of red blood cells and alcohol consumption.
Oral glucose tolerance test	Comprehensively evaluate the blood glucose regulation ability. High diagnostic value.	Cumbersome detection process. Poor patient compliance. Affected by diet, exercise, and stress status.

or CGM-related indices; it can only serve as a complementary biomarker for risk stratification of diabetes complications, working synergistically to improve the glycemic evaluation system.

Basic Characteristics of 1,5-AG

Physiological Characteristics of 1,5-AG

The chemical structure of 1,5-AG is similar to that of glucose, but 1,5-AG lacks a hydroxyl group (-OH) at the C-1 position (Figure 1), and it is a naturally occurring monosaccharide with stable chemical properties.²² 1,5-AG mainly comes from the intake of daily foods, and after absorption through the intestines, it is widely distributed in various tissues and organs of the human body in a free form. Due to its metabolic inertia, it rarely undergoes metabolic degradation in the body.²³ 1,5-AG can also freely enter and exit cells based on the concentration gradient to maintain a dynamic equilibrium, which demonstrates its stability in the body. Most of the 1,5-AG excreted in the urine is reabsorbed in the renal tubules. Since glucose shares the same transport protein with 1,5-AG, there will be competition for reabsorption in the renal tubules. When patients' blood glucose levels exceed the renal glucose threshold (8.9–10.0 mmol/L), reabsorption of 1,5-AG by the renal tubules decreases, resulting in a large amount of 1,5-AG being excreted out of the body with the urine, which ultimately causes a significant decrease in serum 1,5-AG concentrations.²⁴ Changes in 1,5-AG levels mainly reflect hyperglycemic fluctuations when blood glucose exceeds the renal glucose threshold, rather than overall blood glucose variability. Mild or moderate renal insufficiency has no significant effect on 1,5-AG values.²⁵ Hasslacher C et al²⁶ also reported that each 10 mL/min/1.73 m² reduction in estimated glomerular filtration rate was associated with an approximately 0.32 µg/mL decrease in 1,5-AG. Thus, early-stage chronic kidney disease does not impair the efficacy of 1,5-AG for blood glucose assessment. However, when chronic kidney disease progresses to stages 4–5, 1,5-AG is markedly affected and can no longer be used alone to assess blood glucose status. 1,5-AG is highly sensitive to glycemic fluctuations, with a half-life of approximately 1–2 weeks. When the patient's blood glucose is well controlled, the concentration of serum 1,5-AG will gradually increase and reach an equilibrium state in about 5 weeks (Figure 2).²⁷ Thus, 1,5-AG has a significant negative correlation with the hyperglycemic state. It can reflect short-term (in the recent 1–2 weeks) glycemic fluctuations and postprandial hyperglycemia and is closely related to HbA1c, which is expected to provide risk stratification for diabetes complications.^{11,28}

Influencing Factors and Detection Methods of 1,5-AG

Many factors influence 1,5-AG levels, including race, gender, dietary habits, and medications.²⁹ Parrinello CM et al³⁰ discovered that 1,5-AG was significantly lower in the Black race compared to the White race. Additionally, the performance of 1,5-AG in assessing the risk of diabetes complications varied among races. At the same time, there

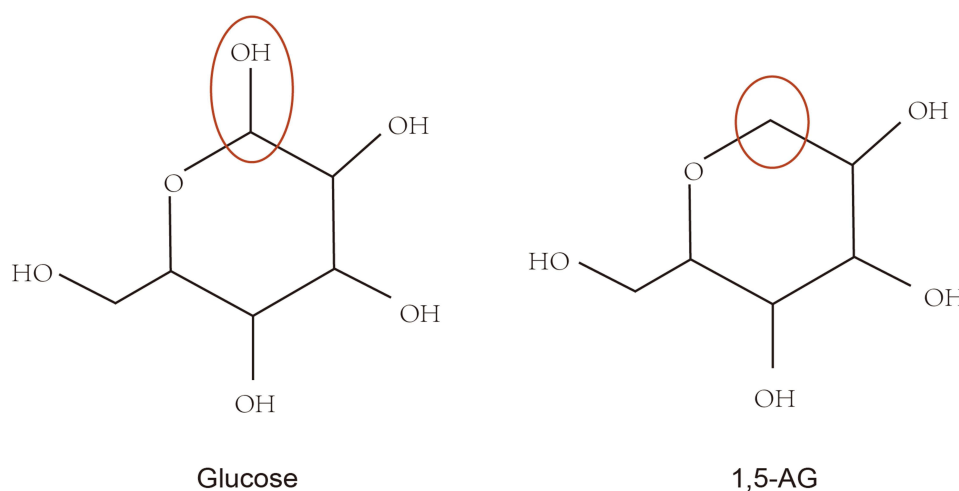


Figure 1 The structure of glucose and 1,5-AG.

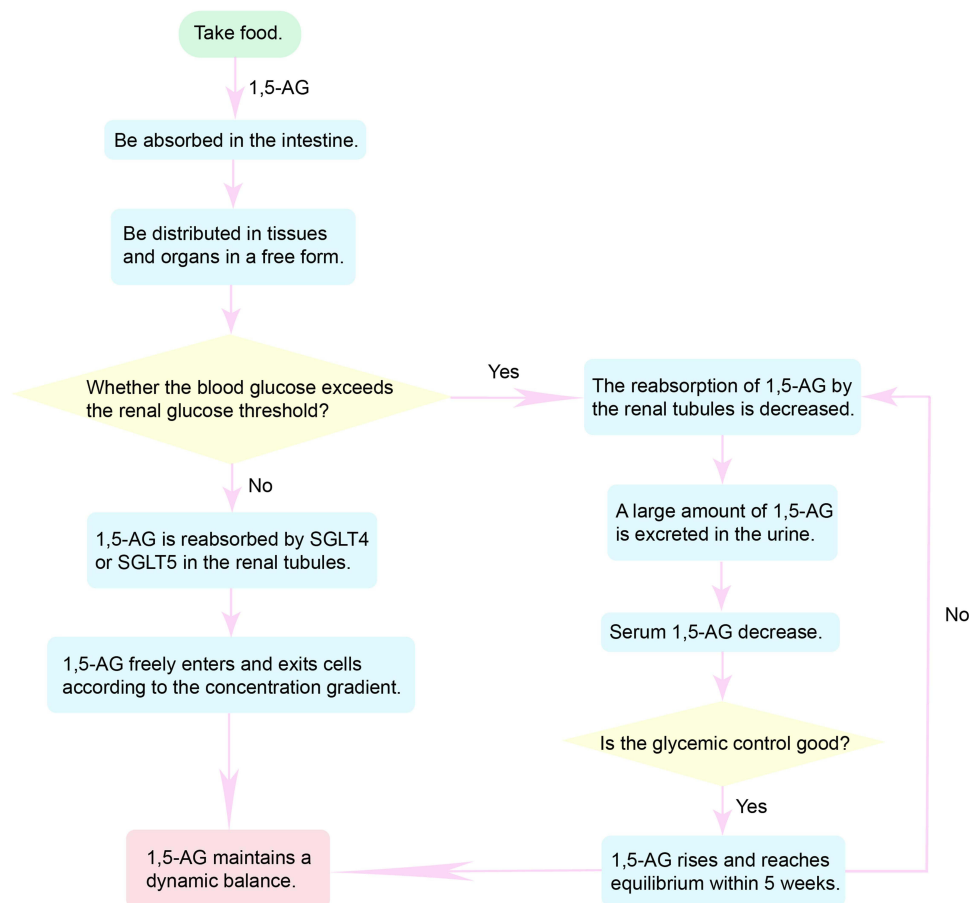


Figure 2 The metabolic mechanism of 1,5-AG.

are obvious gender differences in 1,5-AG levels, with males generally higher than females.³¹ Among the general population, the types and intake of carbohydrates³² can also affect the concentration of 1,5-AG. For example, those who take in dairy products on a regular basis have relatively low serum 1,5-AG levels.³³ Meanwhile, α -glucosidase inhibitors (AGIs) can decrease intestinal absorption of 1,5-AG,³⁴ and sodium glucose cotransporter 2 inhibitors (SGLT2i) can reduce renal tubule reabsorption of 1,5-AG by indirectly inhibiting the transporter protein,³⁵ both of which can lead to a decrease in serum 1,5-AG. Fereidouni S et al³⁶ reviewed 292 cases. Among them, 240 patients were treated with SGLT2i, with a mean 1,5-AG level of 1.2 $\mu\text{g/mL}$, and 92% of these patients had $1,5\text{-AG} \leq 2 \mu\text{g/mL}$; 52 patients did not receive SGLT2i, with a mean 1,5-AG level of 6.4 $\mu\text{g/mL}$, and only 12% of these patients had $1,5\text{-AG} \leq 2 \mu\text{g/mL}$. These findings indicate that SGLT2i can lead to a significant reduction in 1,5-AG levels, so 1,5-AG cannot be directly used to evaluate the glycemic control level of patients receiving SGLT2i treatment. Nevertheless, 1,5-AG still has unique clinical value. A 1,5-AG level $\leq 2 \mu\text{g/mL}$ is an objective indicator of the therapeutic effect of SGLT2i and good patient medication adherence, guiding clinical treatment regimen adjustments. In contrast, traditional Chinese medicines or Chinese patent medicines with high polygala components can increase 1,5-AG levels.³⁷ Although SGLT2i and AGIs can affect 1,5-AG levels, these agents are not administered to the entire population of patients with diabetes undergoing diagnosis and management. In addition, 1,5-AG can reflect short-term glycemic fluctuations, compensate for the limitations of HbA1c, and identify occult postprandial hyperglycemia, thus maintaining important clinical application value. A large number of studies^{7,38} have found that 1,5-AG levels are unaffected by alcohol consumption, hemoglobin, red blood cell lifespan, temperature, and other factors. For patients treated with SGLT2i or AGIs, 1,5-AG should not be used as the sole indicator for evaluating glycemic control status. Instead, a comprehensive assessment combined with FPG, HbA1c, and other indicators is recommended, or 1,5-AG testing can be performed after approximately 4 weeks of

drug discontinuation. Therefore, 1,5-AG can serve as a complementary biomarker, applicable from short-term glycemic monitoring to risk stratification of diabetes complications.

1,5-AG can be quantitatively detected in various biological samples such as serum, cerebrospinal fluid, and saliva. Currently, the main detection methods are categorized into two major groups: mass spectrometry and enzyme assay, and there is a strong correlation between the two.³⁹ Mass spectrometry includes gas chromatography-mass spectrometry,⁴⁰ liquid chromatography-tandem mass spectrometry,⁴¹ and so on. These methods have good sensitivity and high accuracy, but the operation is complicated, and the detection cost is high. Therefore, they are less used in the routine detection of serum 1,5-AG and are more often applied to the analysis of samples with relatively low 1,5-AG content, such as saliva. Commonly used enzyme assay kits include GlycoMark® (GlycoMark, Inc., USA) and Determiner-L (Kyowa Medex, Japan).⁴² These methods have strong specificity, are easy to operate, and have a wider application range. Salivary 1,5-AG detection provides significant advantages, including non-invasiveness and simple sample collection. It can be applied to the risk screening of diabetes complications in large-scale populations, showing high potential for clinical application. However, mass spectrometry's high detection cost limits its application in large-scale screening, while the enzyme assay lacks mature commercialized kits. Relevant studies have found that galactose in the sample interfered with the detection results of saliva 1,5-AG using the GlycoMark® kit, resulting in a lack of correlation between its readings and those measured by mass spectrometry;³⁹ there was also no significant correlation with serum 1,5-AG measured by the GlycoMark® kit.⁴³ Currently, the salivary 1,5-AG assay remains in the stage of clinical research and validation, with relatively low maturity in overall clinical application, and has not yet been adopted into routine clinical practice. Nevertheless, it holds great application potential. In the future, large-sample, multicenter clinical trials can be carried out for further verification so as to promote the clinical translation of this detection technique. In summary, in order to realize the application and popularization of 1,5-AG detection technology, a large number of in-depth studies are still needed in the future to explore more suitable and reliable detection methods.

Reference Range of 1,5-AG in Healthy Population

At present, no unified standard for 1,5-AG has been issued by international authoritative organizations, including the World Health Organization and the International Diabetes Federation. In China, 1,5-AG is only recommended as an auxiliary indicator for glycemic monitoring, without a nationally unified reference interval. As for the units of 1,5-AG, the two mainstream units currently in use are $\mu\text{mol/L}$ and $\mu\text{g/mL}$ (or mg/L), with a conversion relationship of $1 \mu\text{mol/L} = 0.162 \mu\text{g/mL}$. However, no mandatory unified standard has been established worldwide. Nevertheless, we discovered that $\mu\text{g/mL}$ is the most commonly used unit in North America and elsewhere in the world. This unit is relatively standardized and suitable for a wide range of applications; thus, it can be used as the standard unit for 1,5-AG. However, the reference range of 1,5-AG in healthy populations varies significantly, affected by multiple factors such as gender and age.⁴⁴ Nowatzke W et al³⁸ reported that in the American population, the reference range of 1,5-AG for men is 10.2–33.8 $\mu\text{g/mL}$, while for women it is 5.9–31.8 $\mu\text{g/mL}$. This result suggests that gender may be one of the important reasons for the differences in the reference range of 1,5-AG. In the Chinese population, relevant studies have also reached similar conclusions. Li S et al⁴⁵ studied the healthy population in Guangdong Province and found that there were obvious gender differences in the normal reference range of 1,5-AG. For men, it was 34.61–37.37 $\mu\text{g/mL}$, and for women, it was 22.38–25.07 $\mu\text{g/mL}$. This result deviates significantly from the kit's reference range, indicating that in clinical applications, the influence of regional and population differences on the reference range should be fully considered. In addition, Chen C et al³¹ further clarified the gender differences in the reference range of 1,5-AG by conducting OGTT on the healthy population in Jiangsu Province. The results showed that the reference range of 1,5-AG was 15.8–52.6 $\mu\text{g/mL}$ in men and 14.3–48.0 $\mu\text{g/mL}$ in women. Among them, the reference intervals for menopausal and postmenopausal women were 13.9–45.3 $\mu\text{g/mL}$ and 14.6–49.6 $\mu\text{g/mL}$, respectively. This indicates that the reference range of 1,5-AG for women varies depending on their physiological stages.

In addition, systematic errors exist among different detection methods, including the enzyme assay, gas chromatography-mass spectrometry, and liquid chromatography-tandem mass spectrometry, which further compromises the comparability of results. Most existing relevant studies are limited to a single region and ethnic group, and large-sample multicenter studies are still lacking. Therefore, a complete standardized cutoff framework for 1,5-AG cannot be established at present. It is evident that the reference range of 1,5-AG is affected by multiple factors. In clinical practice, a unified detection method should be used as much as possible to reduce inter-method differences. In the future, large-

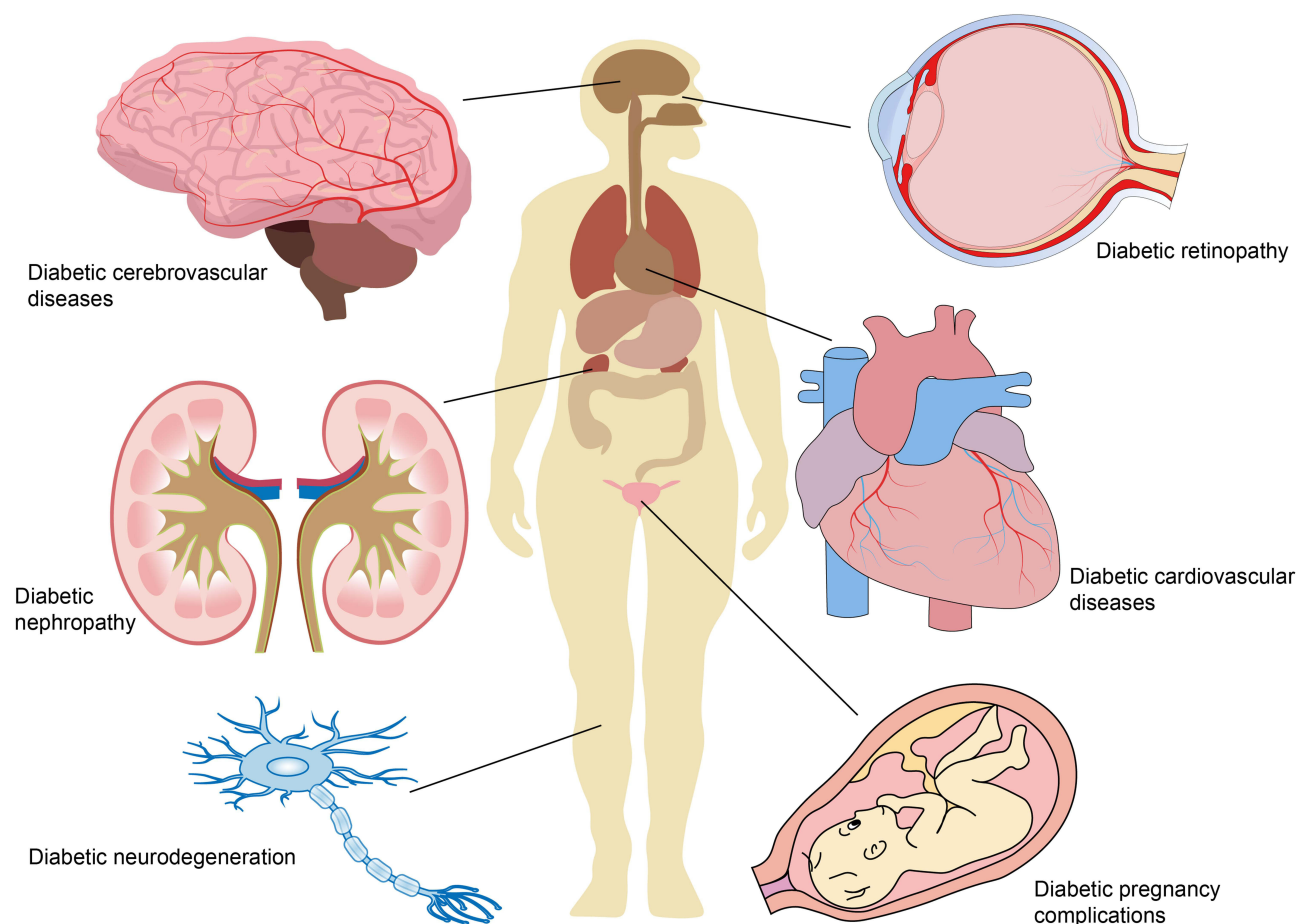


Figure 3 Diabetes complications with 1,5-AG risk stratification value.

sample multicenter studies across multiple regions and ethnic groups can be conducted to establish stratified reference intervals based on sex, age, and ethnicity. This will ensure the accuracy and reliability of test results and further expand the clinical application of 1,5-AG.

Application of 1,5-AG in Diabetes Complications

If the glycemic control of diabetic patients fails to reach the ideal state, it can trigger a series of complications, resulting in impaired function of vital target organs such as the heart, brain, and kidneys (Figure 3). The research results based on relevant mouse models have confirmed the existence of oxidative stress in diabetic patients. When blood glucose levels remain high for a long time, it promotes the increased production of glycosylation products and glucose oxidation products, resulting in an increase in the generation of reactive oxygen species in the body, which is accompanied by a deficiency of superoxide dismutase.⁴⁶ It will induce vascular endothelial cell dysfunction, ultimately leading to the occurrence of microvascular complications.^{47,48} Furthermore, large fluctuations in blood glucose can also cause epigenetic changes, resulting in a decrease in the methylation level of the promoters of relevant transcription genes, aggravating damage to glomerular mesangial and vascular endothelial cells,⁴⁹ which in turn causes renal function impairment and accelerates the progression of diabetic nephropathy (DN). Li Z et al⁵⁰ conducted a 3-month investigation on 71 patients with T2DM and discovered that 1,5-AG was negatively correlated with superoxide dismutase, while FPG and HbA1c were positively correlated. 1,5-AG can effectively reflect the degree of oxidative stress in T2DM patients, which is important for disease monitoring. Tan AC et al⁵¹ divided 836 T2DM patients into three groups: without microvascular complications (n = 490), with one type of microvascular complication (n = 217), and with two or more types of microvascular complications (n = 129). Then detected their serum 1,5-AG and insulin resistance-related indexes. The study found that serum 1,5-AG was significantly higher in the group without microvascular

complications (77.16 $\mu\text{g/mL}$) than in the other two groups (51.05 $\mu\text{g/mL}$ and 30.42 $\mu\text{g/mL}$, respectively), and patients with fewer microvascular complications had higher serum 1,5-AG ($H = 210.020$, $P < 0.001$). Further analysis showed that the decrease of 1,5-AG is consistently associated with the occurrence of microvascular complications at different HbA1c levels. Even in T2DM patients with well-controlled HbA1c, 1,5-AG could still be used as an auxiliary indicator to assess the risk of microvascular complications. This conclusion is consistent with the viewpoint of Lawler PR.⁵² Taken together, 1,5-AG exhibits promising potential for clinical application in the risk stratification of diabetes microvascular complications.

Diabetic Nephropathy

A study⁵³ showed that when the 1,5-AG level in diabetic patients is lower than 6 $\mu\text{g/mL}$, the risk of DN will increase by more than twice. Tavares G et al⁵⁴ suggest that low 1,5-AG levels are linked to the progression of DN and can be used to assess the risk of DN. Lee AK et al⁵⁵ conducted a series of related examinations on 1,206 diabetic patients with a risk of community atherosclerosis. The research results demonstrated that 1,5-AG could be a sensitive marker for capturing kidney damage and cognitive impairment. Higher fluctuations in blood glucose may cause damage to the vascular system and accelerate the progression of DN. Ouchi M et al⁵⁶ also pointed out that 1,5-AG is related to early renal tubular damage in T2DM. In addition, low levels of 1,5-AG are significantly associated with the risk of end-stage renal disease. When reduced 1,5-AG are detected, it indicates recent poor glycemic control. At this time, attention should be focused on screening for kidney damage and implementing early intervention methods to prevent the occurrence of adverse outcomes such as end-stage renal disease.⁵⁷ Ni J et al⁵⁸ detected the glomerular filtration rate and serum 1,5-AG of 5,337 patients with T2DM and found a negative correlation ($r = -0.189$) between them. Thus, 1,5-AG is a reliable marker for evaluating glycemic control in patients with mild or moderate renal insufficiency. Ju YJ et al⁵⁹ recruited 120 patients with stage III DN and found a significant positive correlation ($r = 0.591$) between 1,5-AG and time in range, indicating its potential use as a short-term glycemic control indicator in DN.

Xie W et al⁶⁰ found that among people with $\text{HbA1c} \leq 7.0\%$, the serum 1,5-AG was lower in the abnormal urinary microcreatinine/creatinine ratio group than in the normal group ($P < 0.01$), and the serum 1,5-AG was negatively correlated with urinary microcreatinine/creatinine ratio and FPG. It can be seen that glycemic fluctuations may still exist in T2DM patients with good glycemic control. 1,5-AG can be used to evaluate the short-term glycemic fluctuations, provide additional risk stratification for diabetes complications, and enable early screening and timely intervention, which in turn slows down the development of DN. Okuno T et al⁶¹ proposed that there was an independent correlation between low 1,5-AG levels and the occurrence of microalbuminuria, and that combining 1,5-AG with the FPG coefficient of variation might better assess the risk of developing DN. To sum up, 1,5-AG can not only assess the risk of DN, but also reflect the glycemic control status of patients with impaired renal function.

Diabetic Retinopathy

Peng YF et al⁶² divided 556 T2DM patients into the diabetic retinopathy (DR) group and non-DR group, then detected their serum 1,5-AG, HbA1c, and other indicators. The study found that serum 1,5-AG was significantly lower in the DR group than in the non-DR group ($P < 0.05$). Selvin E et al⁶³ conducted a 20-year follow-up of 10,000 people at risk of community atherosclerosis and found that patients with $1,5\text{-AG} < 6 \mu\text{g/mL}$ had a significantly higher risk of developing DR. The lower the 1,5-AG, the greater the probability of DR, which remained statistically significant after adjusting for HbA1c. Mukai N et al⁶³ included 2,681 subjects to determine the optimal thresholds of various blood glucose indicators for diagnosing DR, including FPG, HbA1c, and 1,5-AG. The results showed that the optimal thresholds for each indicator were FPG: 6.5 mmol/L, HbA1c: 6.1%, and 1,5-AG: 12.1 $\mu\text{g/mL}$. When $1,5\text{-AG} < 12.1 \mu\text{g/mL}$, the risk of DR increased significantly. As a result, monitoring serum 1,5-AG in clinical can effectively assess the risk of DR, allowing for earlier intervention measures, preventing the occurrence of microvascular complications. This view is also supported by Kim WJ et al,⁶⁴ who conducted a 5-year follow-up of 567 T2DM patients. The study found that those with low 1,5-AG ($< 10.0 \mu\text{g/mL}$) had a substantially higher risk of developing DR.

Diabetic Cardiovascular Diseases

Postprandial hyperglycemia and large glycemic fluctuations are important risk factors for coronary artery disease (CAD). But HbA1c primarily reflects average glycemic fluctuations over 3 months; it is insensitive to short-term glycemic fluctuations and

cannot predict cardiovascular diseases in time. In contrast, 1,5-AG can accurately reflect postprandial hyperglycemia and blood glucose variability, and low 1,5-AG is associated with an increased risk of adverse cardiovascular events.⁶⁵ A community-based prospective cohort study discovered that diabetic patients with 1,5-AG < 6.0 µg/mL had a significantly higher risk of cardiovascular diseases, including CAD, ischemic stroke, and heart failure. In addition, when 1,5-AG decreased, patients' mortality risk rose, demonstrating the importance of 1,5-AG in assessing diabetic cardiovascular diseases.⁶⁶ Fujiwara T et al⁶⁷ found an independent correlation between reduced serum 1,5-AG and new-onset CAD in diabetic patients (0.93, 95% CI 0.88–0.98, P = 0.006), while there was no association between HbA1c and CAD. Su G et al⁶⁸ studied 132 diabetic patients with non-ST-segment elevation acute coronary syndromes, who were subjected to 1,5-AG testing and intravascular ultrasound. The results showed that patients with coronary plaque rupture had lower serum 1,5-AG and higher HbA1c, indicating that low 1,5-AG is an independent predictor of coronary plaque rupture in patients with diabetic acute coronary syndromes, which helps to evaluate diabetic patients' cardiovascular outcomes. Thus, by monitoring short-term glycemic fluctuations, 1,5-AG can serve as a complementary biomarker for identifying cardiovascular risk in diabetic patients.

It is well known that high levels of HbA1c are strongly associated with the occurrence of diabetic cardiovascular disease, but there is still a lack of appropriate indicators to assess the risk of cardiovascular diseases in patients with good glycemic control (HbA1c < 7.0%). Ouchi S et al⁶⁹ found that even for patients with HbA1c < 7%, low 1,5-AG was also significantly associated with cardiac mortality (p = 0.02). In a study by Zou YH et al,⁷⁰ 160 patients with unstable angina pectoris and HbA1c < 7.0% were classified into two groups: calcification and non-calcification. Serum 1,5-AG and alkaline phosphatase levels were evaluated in each group. The research showed that 1,5-AG was significantly lower in the calcification group, while alkaline phosphatase was higher. This further confirms that there is a correlation between 1,5-AG levels and coronary artery calcification under the condition of good glycemic control, and low levels of 1,5-AG indicate a higher risk of cardiovascular events in patients.⁷¹ Most studies have indicated that 1,5-AG can assess the risk of diabetic cardiovascular diseases and can serve as a biomarker for monitoring glycemic fluctuations to stratify the risk of complications. These studies adopted diverse designs, including prospective cohort studies, cross-sectional studies, and retrospective cohort studies, and the methodological diversity provides multi-dimensional evidence to support the conclusions. Notably, a small number of studies have presented divergent viewpoints (Table 2). Warren B et al⁷² concluded a negative correlation between low levels of 1,5-AG (< 10 µg/mL) and cardiovascular diseases but noticed

Table 2 Specific Analysis of Different Clinical Study Results in Diabetic Cardiovascular Diseases

Literature	Research Type	Sample Characteristics	Measures	Evaluation Indicators	Research Results
[65]	Prospective cohort study.	141 consecutive patients who underwent percutaneous coronary intervention.	Detect 1,5-AG and HbA1c and observe adverse cardiovascular events during follow-up.	Whether adverse cardiovascular events occur.	Lower 1,5-AG was independently associated with any coronary revascularization and target lesion revascularization, whereas higher HbA1c was not.
[66]	Prospective cohort study.	11,106 participants without cardiovascular disease.	Detect 1,5-AG and follow up for 20 years.	Whether CAD, ischemic stroke, heart failure, and death occur.	Diabetic patients with 1,5-AG < 6.0 µg/mL had a significantly higher risk of cardiovascular diseases, including CAD, ischemic stroke, heart failure, and death.
[67]	Prospective cohort study.	227 consecutive patients who underwent coronary angiography.	Detect HbA1c, glycoalbumin, and 1,5-AG.	Whether CAD occurs.	Low 1,5-AG was independently associated with CAD, and it could identify the risk of CAD in diabetic patients.

(Continued)

Table 2 (Continued).

Literature	Research Type	Sample Characteristics	Measures	Evaluation Indicators	Research Results
[68]	Cross-sectional study.	132 diabetic patients with non-ST-segment elevation acute coronary syndromes.	Underwent intravascular ultrasound examination; detect FPG, HbA1c, and Fasting urinary 8-iso-prostaglandin F2 α .	Whether coronary plaque rupture occurs.	Patients with coronary plaque rupture had lower serum 1,5-AG and higher HbA1c. Low 1,5-AG is an independent predictor of coronary plaque rupture in patients with diabetic acute coronary syndromes.
[69]	Retrospective cohort study.	388 consecutive acute coronary syndrome patients with HbA1c <7%.	Detect 1,5-AG immediately before emergency coronary angiography during a mean follow-up of 46.9 months.	Whether cardiac mortality occurs.	9 patients died of cardiovascular disease, and low 1,5-AG levels were associated with cardiac mortality ($p = 0.02$).
[70]	Retrospective case-control study.	160 patients underwent percutaneous coronary intervention with unstable angina pectoris and HbA1c < 7%.	Divide into calcification and non-calcification groups; detect 1,5-AG and alkaline phosphatase.	Association between 1,5-AG, alkaline phosphatase and coronary artery calcification.	1,5-AG was significantly lower in the calcification group, while alkaline phosphatase was higher.
[72]	Prospective cohort study.	6644 Atherosclerosis Risk in Communities Study participants without diagnosed diabetes.	Follow-up for 20 years; detect 1,5-AG and 2-h glucose.	Incidence of diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality.	When 1,5-AG < 10 $\mu\text{g/mL}$, it is associated with major clinical outcomes with a significant threshold effect and is not superior to 2-h glucose.
[73]	Secondary observational cohort study.	6,807 T2DM patients.	Detect 1,5-AG, hs-cTnT and NT-proBNP; divide patients into three 1,5-AG groups (<6, 6–<10, ≥ 10 $\mu\text{g/mL}$).	Whether microvascular and macrovascular events occur.	1,5-AG was not significantly associated with subclinical myocardial damage and had no value in assessing cardiovascular event risk.

a threshold effect. At higher levels of 1,5-AG, no risk association was found between them, indicating that 1,5-AG has evident limitations. Rooney MR et al⁷³ also believed that the correlation between 1,5-AG and subclinical myocardial injury is not strong, and it cannot be used as a marker for assessing the risk of diabetic cardiovascular disease. However, the specimens used in the ADVANCE trial were measured after approximately 15 years of frozen storage, and there is currently no standardized operating procedure, which may lead to bias in the results. In addition, this study only performed a single baseline measurement, and its reliability remains to be verified. Therefore, the role of 1,5-AG in cardiovascular disease cannot be directly overturned, and a large number of studies are still needed to further validate the clinical value of 1,5-AG in the future.

Diabetic Cerebrovascular Diseases

Ikeda N et al⁷⁴ separated 889 participants into two groups (1,5-AG < 10.0 $\mu\text{g/mL}$ and 1,5-AG ≥ 10.0 $\mu\text{g/mL}$) and studied them for 2–3 years. The study found that people in the 1,5-AG < 10 $\mu\text{g/mL}$ group had a higher risk of major adverse cardiovascular and cerebrovascular events, including stroke. This result remained substantial even in non-diabetic

patients without CAD. Li T et al⁷⁵ found that 1,5-AG was an independent predictor of hyperintense intracranial plaques on T1WI. Low 1,5-AG indicated large glycemic fluctuations, and the probability of intracranial plaques would be significantly higher. Shi CH⁷⁶ included 204 T2DM patients and measured their indicators such as carotid intima-media thickness, 1,5-AG, and HbA1c. It was found that carotid intima-media thickness was negatively correlated with 1,5-AG and positively correlated with HbA1c. Especially for patients with HbA1c $\leq$ 7%, the negative correlation between 1,5-AG and carotid intima-media thickness was more significant. This indicates that decreased 1,5-AG can be used as a biomarker to assess atherosclerosis in diabetic patients. The study by Shiga Y et al⁷⁷ also supported the above view. They found that 1,5-AG can sensitively reflect short-term glycemic fluctuations in patients with well-controlled glycemia. When 1,5-AG < 14 μ g/mL, the risk of acute ischemic stroke or transient ischemic attack was significantly increased.

Diabetic Neurodegeneration

1,5-AG was positively correlated with delayed recall score and may serve as a potential biomarker for assessing cognitive decline.⁷⁸ Yamawaki M et al⁷⁹ carried out an investigation on 688 subjects, who were comprehensively examined for cranial MRI, serum 1,5-AG, and cognitive function. Lower 1,5-AG was found to have a positive correlation with severe periventricular hyperintensity and deep white matter hyperintensity. Reduced 1,5-AG is an important risk factor for cognitive impairment and depression, and measuring 1,5-AG levels can help detect the risk of cognitive dysfunction and severe hypoglycemia.⁵⁵ As a result, 1,5-AG is believed to have a significant role in assessing the risk of diabetic neurodegeneration. Rawlings AM et al⁸⁰ measured the cognitive function and 1,5-AG levels of 12,996 subjects through a 20-year follow-up study. The study found that in diabetic patients, for every 5 μ g/mL decrease in 1,5-AG, the risk of dementia increased by 16%, whereas no significant association was seen in nondiabetic patients. This indicates that a decreased level of 1,5-AG is associated with cognitive dysfunction and a higher risk of dementia. Monitoring serum 1,5-AG allows for the early assessment of cognitive dysfunction, prompting clinicians to take appropriate interventions, delay disease progression, and improve patients' quality of life.⁸¹ Mukai N et al⁸² conducted a 4.8-year follow-up on 1,187 Japanese subjects aged $\geq$ 65 years without dementia. The study found that 1,5-AG showed a poor correlation with cognitive decline such as Alzheimer's disease (Table 3). However, this study had

Table 3 Specific Analysis of Different Clinical Study Results in Diabetic Neurodegeneration

Literature	Research Type	Sample Characteristics	Measures	Evaluation Indicators	Research Results
[78]	Cross-sectional study.	80 healthy subjects.	Detect 1,5-AG, FPG, HbA1c, and 2-h glucose; assess MoCA, SAS, and GDS.	Whether mild cognitive impairment occurs.	Negatively correlated with FPG, 2-h glucose, and HbA1c; positively correlated with 1,5-AG. 1,5-AG is a potential biomarker of cognitive decline.
[79]	Cross-sectional study.	668 elderly individuals aged $\geq$ 65 years.	Comprehensive evaluation including cranial MRI, 1,5-AG, Fazekas score, and GDS.	Classified by severity of periventricular hyperintensities and deep white matter hyperintensities.	Lower 1,5-AG was positively associated with severe periventricular hyperintensities and deep white matter hyperintensities.
[80]	Prospective cohort study.	12,996 participants from the Atherosclerosis Risk in Communities study.	Follow up for 20 years; detect 1,5-AG and HbA1c.	Dementia ascertainment; assess cognitive function by z-scores.	In diabetic patients, each 5 μ g/mL reduction in 1,5-AG led to a 16% higher risk of dementia.

(Continued)

Table 3 (Continued).

Literature	Research Type	Sample Characteristics	Measures	Evaluation Indicators	Research Results
[80]	Cross-sectional study.	160 elderly patients with T2DM.	Detect 1,5-AG and HbA1c.	Assess cognitive function by MoCA.	1,5-AG positively correlated with cognitive function; lower 1,5-AG linked to higher cognitive impairment risk in T2DM patients.
[82]	Prospective cohort study.	1187 Japanese adults aged ≥ 65 years without dementia.	Follow up for an average of 4.8 years; assess HbA1c, 1,5-AG, and glycated albumin.	Whether Alzheimer's disease occurs.	Elevated glycated albumin/HbA1c ratio significantly associated with Alzheimer's disease risk; 1,5-AG and HbA1c not associated with Alzheimer's disease.

limitations: it confined the population to Japanese, failed to fully consider the racial differences in 1,5-AG, and only selected older patients, resulting in certain selection bias. In addition, the relevant literature is relatively scarce, which is insufficient to refute the current conclusion. Nevertheless, this provides us with insights to further examine whether 1,5-AG can offer risk stratification for diabetic neurodegeneration. In the future, more in-depth and comprehensive studies are still needed to clarify its potential value and application prospects.

Diabetic Pregnancy Complications

In addition to the above vascular complications, Saglam B et al⁸³ found that 1,5-AG values were correlated with post-load glucose values in pregnant women, which could be used as a potential biomarker for assessing the risk of gestational diabetes mellitus (GDM). Pramodkumar TA et al⁸⁴ recruited 220 pregnant women, of whom 145 did not have GDM and 75 had GDM, and then measured their serum 1,5-AG individually. The results found that the average value of 1,5-AG in pregnant women with GDM was 11.8 ± 5.7 $\mu\text{g/mL}$, lower than that in pregnant women without GDM (16.2 ± 6.2 $\mu\text{g/mL}$). This result strongly confirmed the significant correlation between 1,5-AG and GDM. Salem MM et al⁸⁵ conducted the OGTT on pregnant women and detected 1,5-AG in the first trimester of pregnancy and at ≥ 24 weeks of pregnancy. The results showed that lower 1,5-AG (< 7.55 $\mu\text{g/mL}$) in the first trimester of pregnancy indicates higher GDM risk (sensitivity 100%, specificity 80%). It can be seen that measuring 1,5-AG in the first trimester of pregnancy is a good biomarker for assessing the risk of GDM. Clinicians can take timely intervention measures according to the test results, which is of vital significance for reducing the incidence of GDM.

Furthermore, low levels of 1,5-AG are significantly associated with adverse pregnancy outcomes.^{86,87} Monitoring 1,5-AG can identify the risk of diabetic pregnancy complications, which helps reduce the occurrence of such complications.⁸⁸ Yefet E et al⁸⁹ detected indicators such as 1,5-AG, HbA1c, glycated albumin, and fructosamine in pregnant women with diabetes ($n = 70$) and without diabetes ($n = 35$). The results showed that only 1,5-AG was negatively correlated with diabetic pregnancy complications such as large for gestational age (LGA) and neonatal hypoglycemia, while other markers were not associated with them. Wright LA et al⁹⁰ included 17 patients with GDM, 48 patients with T1DM, and 37 patients with T2DM, monitored 1,5-AG and HbA1c throughout pregnancy, and analyzed their relationships with diabetic pregnancy complications. The study found a negative linear correlation between 1,5-AG levels and the z-score of neonatal weight ($R = -0.28$, $P = 0.005$), which can be used to assess LGA, while HbA1c was weakly correlated. Meanwhile, the study have also demonstrated that 1,5-AG levels in individuals with neonatal hypoglycemia were lower than those without neonatal hypoglycemia ($P=0.08$). This further highlights that 1,5-AG can be used for risk stratification of diabetic pregnancy complications, especially for LGA and neonatal hypoglycemia. Nowak N et al⁹¹ studied 82 pregnant women with T1DM and found that 1,5-AG was closely related to the continuous glucose monitoring system index. Decreased 1,5-AG levels were associated with increased neonatal weight gain, which would increase the risk of macrosomia. Especially in the third trimester of pregnancy, 1,5-AG was the strongest predictor

of macrosomia. However, some studies have found that 1,5-AG cannot accurately stratify the risk of GDM, nor can it identify the risk of adverse pregnancy outcomes including macrosomia and neonatal hypoglycemia.⁹² Soffer MD⁹³ also believed that 1,5-AG undergoes physiological reduction during pregnancy, so it cannot be used to assess blood glucose levels in pregnant women and is not an effective biomarker for identifying the risk of GDM. This study is inconsistent with the results of previous studies (Table 4). However, its sample size is limited, with only 50 subjects followed up

Table 4 Specific Analysis of Different Clinical Study Results in Diabetic Pregnancy Complications

Literature	Research Type	Sample Characteristics	Measures	Evaluation Indicators	Research Results
[83]	Cross-sectional case-control study.	80 pregnant women: 40 with GDM and 40 with normal glucose tolerance.	Perform OGTT and detect HbA1c, 1,5-AG, and glycated albumin.	FPG $\geq$ 5.1 mmol/L, 1-h glucose $\geq$ 10 mmol/L, or 2-h glucose $\geq$ 8.5 mmol/L was diagnosed as GDM.	In the GDM group, HbA1c was increased and 1,5-AG was decreased. 1,5-AG was negatively correlated with 1-h glucose.
[84]	Cross-sectional study.	220 pregnant women.	Perform OGTT and detect Fructosamine, 1,5-AG, and HbA1c.	1,5-AG levels and GDM status diagnosed by OGTT.	1,5-AG was significantly lower in pregnant women with GDM, and 1,5-AG was independently associated with GDM.
[85]	Case-control study.	50 pregnant women: 25 high-risk for GDM, 25 non-high-risk.	Detect FPG, adiponectin and 1,5-AG.	Whether 1,5-AG can assess the risk of GDM.	Lower 1,5-AG ($< 7.55 \mu\text{g/mL}$) indicates higher GDM risk and is useful for GDM glycemic monitoring.
[89]	Prospective cohort study.	105 pregnant women: 70 diabetic, 35 nondiabetic.	Detect 1,5-AG, fructosamine, and HbA1c in the diabetic group at baseline, 4–6 weeks post-treatment, and delivery.	Whether they have diabetic pregnancy complications including LGA and neonatal hypoglycemia.	1,5-AG was inversely associated with diabetic pregnancy complications at all time points. Lower 1,5-AG indicated poorer glycemic control and a higher incidence of diabetic pregnancy complications.
[90]	Retrospective cohort study.	102 pregnant women: 17 GDM, 48 T1DM, and 37 T2DM.	Monitor 1,5-AG and HbA1c throughout pregnancy.	Whether diabetic pregnancy complications including low neonatal birth weight occur.	1,5-AG was negatively correlated with neonatal birth weight z-scores and lower 1,5-AG in women whose infants had neonatal hypoglycemia.
[91]	Prospective cohort study.	82 pregnant women with T1DM.	Monitor 1,5-AG and HbA1c, collect CGMS glucose data throughout pregnancy.	Whether macrosomia occurs.	1,5-AG was strongly correlated with CGMS glucose indices. In the third trimester, 1,5-AG had an AUC of 0.81 for predicting macrosomia, higher than HbA1c (0.69).
[92]	Prospective cohort study.	954 obese pregnant women (BMI $\geq 30 \text{ kg/m}^2$).	Detect 1,5-AG at 14–20 and 24–28 weeks of gestation to diagnose GDM.	Whether adverse pregnancy outcomes such as macrosomia and neonatal hypoglycemia occur.	1,5-AG showed moderate diagnostic performance for GDM, but there was no significant association between 1,5-AG and adverse pregnancy outcomes.

(Continued)

Table 4 (Continued).

Literature	Research Type	Sample Characteristics	Measures	Evaluation Indicators	Research Results
[93]	Prospective cohort study.	50 pregnant women and non-pregnant controls.	Pregnant group: detect 1,5-AG and OGTT at 13 weeks, 26 weeks of gestation, and postpartum. Control group: detect once.	Changes in 1,5-AG levels during pregnancy.	1,5-AG is physiologically reduced during pregnancy and cannot be used to assess blood glucose levels in pregnant women.

during pregnancy, so its results may be biased. Nevertheless, large-sample and multi-center clinical studies based on this are still needed in the future to explore the efficacy of 1,5-AG in predicting diabetic pregnancy complications.

Summary and Prospect

1,5-AG is not affected by hemoglobin, red blood cell lifespan, alcohol consumption, or other interfering factors. It can sensitively reflect short-term glycemic fluctuations and postprandial hyperglycemia, effectively compensating for the limitations of traditional indicators, and shows great potential in risk stratification of diabetes complications. 1,5-AG, a new type of glycemic monitoring indicator, has the unique advantage of sensitively reflecting short-term glycemic fluctuations and postprandial hyperglycemia, which can effectively make up for the deficiencies of the traditional indicators, and has shown great potential in predicting diabetes complications. However, there are various detection methods for serum 1,5-AG. Among them, mass spectrometry has high detection accuracy, but the operation process is cumbersome and the cost is high. The enzyme is relatively simple and easy to perform, but the detection results are easily affected by factors such as the reagent kit. Therefore, a unified detection method has not been established yet. In addition, 1,5-AG is affected by various factors such as age, gender, and diet, resulting in the unclear definition of its normal reference range. In the future, more large-sample studies are also needed to standardize the normal reference range of serum 1,5-AG.

There continues debate regarding whether 1,5-AG can assess the risk of diabetic cardiovascular diseases, diabetic neurodegeneration, and diabetic pregnancy complications. Currently, the number of relevant studies is relatively small, and there is a lack of large-sample prospective cohort studies, which makes the existing research conclusions less persuasive. Existing studies differ in terms of sample size, operational procedures, and evaluation systems. This methodological heterogeneity may be an important reason for the divergences in conclusions, so it is impossible to jump to conclusions for the time being.

It is well known that HbA1c and FPG can predict diabetic complications. Can 1,5-AG provide additional risk stratification information? The answer is yes. HbA1c only reflects long-term glycemic control over the past 3 months, while FPG merely represents instant blood glucose status at a single time point. Both have obvious limitations in clinical evaluation. As mentioned earlier, patients who have achieved the HbA1c target (<7.0%) may still experience short-term glycemic fluctuations and postprandial hyperglycemia. Sustained abnormal glucose fluctuations directly accelerate the onset and progression of diabetic complications. Relying solely on HbA1c and FPG for complication risk assessment can easily lead to the occult progression of complications in some high-risk individuals, as well as the failure to diagnose high-risk conditions. In contrast, 1,5-AG can effectively identify postprandial hyperglycemia and glycemic variability and compensate for the core deficiencies of traditional blood glucose indicators. As a complementary biomarker, it enables secondary risk stratification of patients on the basis of HbA1c and FPG; monitors glycemic status more sensitively; and identifies potential high-risk populations that cannot be detected by conventional indicators. Early intervention in patients with reduced 1,5-AG levels can effectively block or delay the progression of complications, demonstrating important clinical application value. Li Z et al⁹⁴ also found that the combination of 1,5-AG with other traditional blood glucose and lipid detection indicators could improve the sensitivity and specificity of the diagnosis of DN. Tano S et al⁹⁵ concluded that the combined application of 1,5-AG and HbA1c for monitoring glycemic abnormalities can improve the early risk assessment of GDM. Nowak N et al⁹¹ also reported

that the predictive performance of 1,5-AG combined with HbA1c for macrosomia was higher, with an AUC reaching 0.84. Emerging evidence suggests that biomarkers reflecting short-term glycemic variability, such as 1,5-AG, may play a complementary role when integrated with advanced risk prediction frameworks. Recent studies using CGM and machine learning approaches have demonstrated improved identification of individuals at high risk for diabetes-related complications by capturing dynamic glucose patterns that are not reflected by conventional markers alone. Integrating 1,5-AG with CGM-derived metrics and data-driven predictive models, as illustrated by Montaser E et al,⁹⁶ may enhance early risk stratification and support timely intervention strategies. Such combined approaches could be particularly valuable for preventing or delaying the progression of microvascular complications, including diabetic retinopathy, and warrant further investigation in prospective, large-scale studies. However, there is currently little relevant research on different complications, and the majority are single-center, small-sample, observational studies limited to a specific ethnicity or location, with substantial heterogeneity across studies. Meanwhile, obvious differences exist among studies in detection methods, measurement units, baseline characteristics of the study population, and diagnostic criteria for complications. These lead to substantial discrepancies in the reported cutoff values and poor comparability of results. Consequently, no unified 1,5-AG cutoff value for predicting complication risk has been established, which also limits the clinical application of 1,5-AG. In the future, large-sample, multicenter, multi-ethnic prospective cohort studies combined with CGM and traditional glycemic markers can be conducted to effectively validate the clinical application value of 1,5-AG and determine its optimal cutoff values for various diabetes complications.

In recent years, saliva testing has received widespread attention in clinical research due to its noninvasiveness and simplicity. Jian CH et al⁹⁷ recommended collecting saliva samples by chewing a cotton swab 40–50 times within 1 minute. This sample can be stored for a short period of time at room temperature or at 4°C before being accurately detected by liquid chromatography-mass spectrometry. The results suggested that the normal reference range for salivary 1,5-AG was 0.09–1.63 µg/mL,⁹⁸ which was unaffected by age or gender. However, the enzyme assay for salivary 1,5-AG has not been perfected yet, and more in-depth research is still needed to develop a more suitable detection method. In the future, non-invasive salivary detection is expected to enable better risk stratification for diabetes complications and further improve the clinical application value of 1,5-AG.

Abbreviations

1,5-AG, 1,5-Anhydroglucitol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; OGTT, oral glucose tolerance test; CGM, continuous glucose monitoring; TIR, time in range; GV, glycemic variability; MAGE, mean amplitude of glycemic excursions; T2DM, type 2 diabetes mellitus; SGLT2i, sodium glucose cotransporter 2 inhibitors; AGIs, α -glucosidase inhibitors; DN, diabetic nephropathy; DR, diabetic retinopathy; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; GDM, gestational diabetes mellitus; LGA, large for gestational age.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analyzed in this study.

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Author Contributions

Huijuan Xu: Conceptualization, Writing – original draft, Writing – review & editing. Qiwei Tang: Conceptualization, Writing – original draft, Writing – review & editing. Qiu Chen: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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