MedCrave
Step into the World of Research

Endocrinology & Metabolism International Journal

Clinical & Translational Research

Open Access

CrossMark

Time-in-Range Vs. HbA1c: Is it time to retire the gold standard?

Abstract

Background: Glycated hemoglobin (HbA1c) has long been considered the gold standard for evaluating long-term glycemic control in patients with diabetes mellitus. However, emerging technologies and evolving clinical priorities have led to increasing attention on Time-in-Range (TIR), a continuous glucose monitoring (CGM)-derived metric, as a complementary or potentially superior alternative to HbA1c. TIR offers a dynamic assessment of glucose fluctuations, providing granular insights into daily glycemic variability that may be more reflective of real-world glycemic exposure and associated risks.

Objective: ①This article critically evaluates the role of HbA1c as the longstanding biomarker of glycemic control, its biochemical underpinnings, diagnostic limitations, and its correlation with complications, ② how does TIR, as measure by CGM, compare with HBA1c in predicting glycemic control and long term diabetes complication in individuals with diabetes, ③ moreover It also examines the clinical relevance, interpretation, and potential integration of TIR as a routine clinical metric, while exploring the current limitations, evidence base, and prospects of CGM-based analytics.

Volume 13 Issue 2 - 2025

Saadi JS Al Jadir
Ministry of Higher Education, Iraq

Correspondence: Saadi AlJadir, MB ChB, PhD, MRCP, FACE, FRCP(London), FRCP(Glasgow), Ministry of Higher Education, Iraq, Tel +964 781 390 2926

Received: July 24, 2025 | **Published:** August 08, 2025

Methods: A detailed narrative review was conducted synthesizing historical, biochemical, and clinical evidence supporting the use of HbA1c. Emerging data from international consensus guidelines and landmark studies were analysed to elucidate the clinical utility of TIR. Comparative analyses of TIR and HbA1c were explored using illustrative case studies and CGM reports, with emphasis on glycemic variability, hypoglycemia risk, and patient-centred outcomes.

A PRISMA flow diagram will be used to report the screening and selection process

Structured PICO framework

i. **Population (P)** Individual with T1, Type 2 Diabetes and Type 1.5 (LADA)

ii. **Intervention (I)** TIR measured by CGM

iii. **Comparison (C)** glycated Hemoglobin

iv. **Outcome (O)** Estimation of glycemic Control, incidence of diabetes-related complications (e.g., retinopathy, nephropathy, mortality), and clinical decision-making relevance

Systemic search strategy: a structured literature search will be conducted to identify studies comparing TIR and HBA1c for assessing glycemic control and predicting diabetes related complications.

Database of the search: PubMed/MEDLINE, Scopus, Embase, Cochrane Library, and Google Scholar.

Search Period Jan 2015-July 2025

Inclusion criteria: Studies including children, adults (≥ 18 years) with T1, T2 DM, and LADA; original research, clinical trials, or systematic review: studies comparing TIR and HbA1c in terms of glycemic control and outcomes

Exclusion criteria: Studies focused on gestational diabetes or prediabetes individuals

Secondary research strategy

1) Does TIR provide a stronger correlation with micro or macrovascular complications compared to HbA1c?

2) Which patients' populations (pregnant women, CKD, elderly) is TIR considered a more reliable metric than HbA1c

3) What are the methodological or technical limitations of utilizing TIR across different CGM systems in research, as well as in clinical practice

Results: While HbA1c offers a retrospective average of glucose levels over 2–3 months, it fails to capture glycemic excursions and variability, and is influenced by non-glycemic factors such as hemoglobinopathies, renal dysfunction, and erythrocyte turnover. Conversely, TIR provides real-time, actionable data, correlates strongly with microvascular complications, and aligns more closely with patient perception and therapeutic outcomes. Clinical studies suggest a 10% increase in TIR is associated with a significant reduction of 40-64% in microvascular complications like retinopathy, nephropathy, and neuropathy compared to HbA1c alone.

Evidence is emerging, though less robust, that some studies' TIR may predict macrovascular complications risk (e.g., carotid intima-media thickness, cardiovascular events), but HbA1c remains the established metric in this domain.

Patient population where TIR is considered more reliable; Pregnant women predict better short-term glycemic control, which is critical for fetal outcome. CKD Patients' HbA1c might be inaccurate due to anemia, uremia, and altered erythrocyte life span, whereas TIR can overcome these confounders. In the elderly population, HbA1c may overestimate control due to age-related changes in the glycation process, while TIR offers more reliable real-time insight and hence avoids hypoglycemia. Despite its promise, TIR lacks universal standardization, and inter-device variability remains a concern. Moreover, robust longitudinal outcome data are still emerging.

Conclusion: While HbA1c remains indispensable for diabetes diagnosis and longitudinal population-level assessment, TIR enhances clinical decision-making through its nuanced portrayal of daily glycemic control. Despite its promise, TIR lacks universal standardization, and inter-device variability remains a concern. Moreover, robust longitudinal outcome data are still emerging. TIR should not be viewed as a replacement for HbA1c but rather as a powerful adjunct that facilitates individualized therapy, improves patient engagement, and supports precision medicine in diabetes care. Ongoing efforts in CGM standardization, education, and outcome-based validation are essential before TIR can be universally adopted as a co-primary glycemic metric in clinical guidelines.

Keywords: HbA1c, time-in-range, continuous glucose monitoring, glycemic variability, diabetes mellitus, biomarkers, glucose control, CGM metrics, fructosamine, glycated albumin, 1,5-anhydroglucitol

Abbreviations: TIR, Time-in-range; CGM, continuous glucose monitoring; GGT, glucose tolerance test; ADA, American diabetes association; HPLC, high-performance liquid chromatography; FBG, fasting blood glucose; DPNP, diabetic peripheral neuropathy; CKD, chronic kidney disease; HT, hypertension; NAFLD, non-alcoholic fatty liver disease; eAG, estimated average glucose

Introduction

Diabetes mellitus remains one of the most prevalent and challenging chronic diseases globally, with a continually rising burden of morbidity, mortality, and healthcare costs. Central to the management of diabetes is the accurate and reliable assessment of glycemic control. For decades, glycated hemoglobin (HbA1c) has served as the cornerstone biomarker for this purpose. Introduced into clinical use in the late 20th century following its initial biochemical characterization by Kunkel and Wallenius in 1955, HbA1c reflects the average blood glucose levels over the preceding 8–12 weeks through non-enzymatic glycation of hemoglobin. Strong epidemiological correlations with microvascular complications, combined with the convenience of a single, fasting-independent measurement, reinforced its adoption.

Despite its widespread use and standardization by programs such as the National Glycohemoglobin Standardization Program (NGSP) and endorsement by global entities including the American Diabetes Association (ADA) and the World Health Organization (WHO), HbA1c is not without limitations. A1c values can be significantly affected by conditions altering erythrocyte lifespan, hemoglobin variants, chronic kidney disease, pregnancy, and acute blood loss. Moreover, HbA1c fails to capture short-term glycemic variability, acute excursions, and hypoglycemic events—all of which are increasingly recognized as clinically significant contributors to diabetes-related complications, particularly cardiovascular morbidity, cognitive decline, and diminished quality of life.

With the advent and maturation of continuous glucose monitoring (CGM) systems, a paradigm shift is emerging in diabetes care. CGM technologies provide near real-time interstitial glucose readings, enabling a more granular, patient-centred assessment of glycemic control. A key metric derived from CGM is Time-in-Range (TIR), defined as the percentage of time an individual's glucose levels remain within a target range, typically 70–180 mg/dL (3.9–10 mmol/L) for most adults with type 1 and type 2 diabetes. TIR offers an intuitive, visualizable, and immediate reflection of daily glycemic control, accounting for fluctuations, glycemic variability, and exposure to hypo- or hyperglycemia.

Rising evidence suggests a strong inverse linear correlation between TIR and HbA1c levels, with each 10% increase in TIR leading to approximately a 0.8% decrease in HbA1c. More importantly, recent clinical data demonstrate that higher TIR values are associated with significant reductions in the risk of diabetic complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease. These findings have prompted an international consensus supporting the integration of TIR as a clinical target alongside HbA1c, particularly in individuals utilizing intensive insulin therapy or at high risk for glycemic instability.

This article critically examines the biochemical foundations, diagnostic utility, and clinical limitations of HbA1c, juxtaposed with the practical applications and predictive validity of Time in Range (TIR). We explore whether TIR can—and should—replace HbA1c as the primary metric for glycemic monitoring and control. Through case-based illustrations, a review of clinical guidelines, and an analysis of current evidence, we propose a balanced framework that supports the complementary use of both markers to optimize diabetes management.

Glycated hemoglobin (HbA1C)

HbA1c has long been regarded as the gold standard and a clinical milestone for evaluating glucose control. It remains a useful, economical, and practical tool for long-term glycemic monitoring in patients with diabetes. In March 2009, the World Health Organization (WHO) convened an expert consultation, during which a systematic review was conducted to assess the validity of HbA1c as a diagnostic tool for diabetes mellitus.

The findings of the review were summarized and evaluated via the GRADE method (Grading of Recommendations Assessment, Development and Evaluation). Based on this analysis, an HbA1c value of 6.5% was recommended as the diagnostic cut-off for diabetes. However, a value below 6.5% does not exclude diabetes if diagnosed by other criteria, such as the glucose tolerance test (GGT). The expert panel determined that there is currently insufficient evidence to provide firm recommendations for interpreting HbA1c values below 6.5%.

The American Diabetes Association (ADA) has approved the use of HbA1c assays certified by the National Glycohemoglobin Standardization Program (NGSP), which utilizes techniques such as high-performance liquid chromatography (HPLC). Nevertheless, for achieving high diagnostic precision, fasting blood glucose (FBG) and Glucose Tolerance Test (GGT) remain essential complementary tools.[1–4]

HbA1c and diabetes diagnosis

Hyperglycemia and hypoglycemia are two of the most critical challenges in diabetes management, and effectively controlling these fluctuations is essential for reducing the risk of long-term complications. Such complications include diabetic peripheral neuropathy (DPNP), chronic kidney disease (CKD), dyslipidemia, hypertension (HT), non-alcoholic fatty liver disease (NAFLD), and dementia.[5,6]

HbA1c reflects the percentage of hemoglobin that has been glycated in the blood over the preceding two to three months.[7] The higher the percentage, the more glucose is attached to the hemoglobin molecule, and consequently, the higher the average blood glucose level. In addition to its role in glycemic monitoring, the HbA1c test is also used to diagnose diabetes based on well-established thresholds:

1) If your HbA1c level is below 5.7%, you have a low risk for developing prediabetes or type 2 diabetes.
2) An HbA1c level between 5.7% and less than 6.4% may indicate a diagnosis of prediabetes.
3) A value of 6.5% or higher is diagnostic of type 2 diabetes (Figure 1).[8,9]

Figure 1 HbA1c Thresholds for diabetes diagnosis.

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J.* 2025;13(2):46–61.
DOI: 10.15406/emij.2025.13.00370

Relationship between HbA1c, IFCC Units, and estimated Average Glucose (eAG)

Currently, HbA1c is measured using three main assay methods: immunoassay, cation-exchange high-performance liquid chromatography (HPLC), and Boronate affinity HPLC.[10,11] The results are reported as a percentage, signifying the proportion of glycated hemoglobin (HbA1c) relative to total hemoglobin (HbA). Most clinical laboratories use a reference range for HbA1c between 4.0% and 6.0%, which is considered normal for non-diabetic individuals.[12]

To facilitate the interpretation of HbA1c in terms of daily glucose management, an equation has been developed to estimate the mean blood glucose level:

Estimated mean blood glucose (mg/dL) = HbA1c (%) × 28.7 – 46.7.[13,14]

This conversion allows clinicians and patients to better understand what the percentage value means in practical terms. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) plays a significant role in the global standardization of such measurements (Table 1).[15,16]

Table 1 Correlation between HbA1c, IFCC Units, and estimated Average Glucose (eAG)

HbA1c (NGSP/ DCCT) %	HbA1c (IFCC) mmol/mol	Estimated Average Glucose (eAG) mg/dL
5	31	97
6	42	126
7	53	154
8	64	183
9	75	212
10	83	240
11	96	269
12	107	298
13	118	355

History and biochemistry of HbA1c

The glycated hemoglobin (HbA1c) test serves as the foundation of long-term glycemic monitoring and remains a practical, economical, and widely used tool in diabetes management. The compound was first described in 1955 by Kunkel and Wallenius, who identified HbA1c as a minor subfraction of adult haemoglobin.[17] It wasn't until the 1970s that its role as a reliable marker of average glycemia was fully recognized.[18]

Biochemically, HbA1c is a conjugated heteroprotein formed through the non-enzymatic glycation of hemoglobin. This post-translational process, also known as the Maillard reaction, occurs when glucose binds irreversibly to the N-terminal valine of the beta-chain of hemoglobin, forming a stable Amadori product.[19] If this glycation process progresses, it leads to the formation of advanced glycation end products (AGEs) (Figure 2).[20]

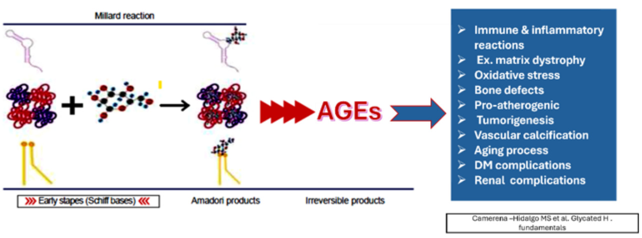

Figure 2 Formation of Advanced Glycation End Products (AGEs) and their biological consequences, courtesy of Camareha-Hidalgo MS, et. al[18]

AGEs contribute to widespread protein modifications across various tissues and play a significant role in diabetes-related complications by promoting inflammatory responses through receptor-mediated pathways.[21] Clinical data have shown that maintaining HbA1c levels below 7% is associated with a reduced risk of both microvascular and macrovascular complications. Therefore, consistent evaluation and monitoring of HbA1c remain critical for effective long-term glycemic control and prevention of disease progression.[7,22]

Pathway of Advanced Glycation End Products (AGEs) formation and their biological effects

Advanced glycation end products (AGEs) are produced not only through endogenous metabolic processes but are also found in processed foods and beverages. Additionally, their formation is influenced by factors such as aging, exposure to ultraviolet radiation, tobacco smoke, various chemical agents, and air pollution, among others.[23]

Glycation vs. glycosylation

It is important to distinguish between glycation and glycosylation, as these are fundamentally different biochemical processes with varying clinical implications. Glycation is a non-enzymatic, irreversible reaction in which free glucose or other reducing sugars bind to the amino groups of proteins, resulting in the formation of brown polymers, a phenomenon known as the Maillard reaction. Such a reaction depends on the concentration of the sugar substrate and results in the formation of a ketoamine structure at the N-terminal of the hemoglobin beta-chain.[24,25] Not only proteins but also nucleic acids and lipids, both intracellular and extracellular, can be altered by glycation, contributing to structural and functional impairments.[25]

In contrast, glycosylation is an enzymatic post-translational modification in which carbohydrates are covalently attached to proteins, lipids, or nucleic acids.[26] This highly regulated process involves specific enzymes that guide the attachment of sugars to amino acid residues such as serine, asparagine, or hydroxylysine. Glycosylation is essential for normal biological functions, including protein folding, trafficking, and stabilization.[27]

However, when glycosylation pathways are disrupted, it can lead to severe pathological consequences. Abnormal glycosylation has been associated with immune dysfunction, chronic inflammation, extracellular matrix abnormalities, and enhanced tumor metastasis. Thus, while glycation is generally harmful and associated with chronic disease, glycosylation is vital for maintaining cellular and systemic homeostasis (Table 2).[28–30]

Table 2 Key differences between glycation and glycosylation, courtesy of Lakna Nov.21, 2018.[26]

Category	Glycation	Glycosylation
Definition	Bonding of a sugar molecule to a protein or lipid molecule without enzymatic regulation	Controlled enzymatic modification of an organic molecule, especially a protein, by the addition of a sugar molecule
Location	Covalent addition of free sugars to the proteins in the bloodstream	A type of post-translational modification, which occurs either in the endoplasmic reticulum or the Golgi apparatus
Modification Type	A type of non-enzymatic modification	A type of enzymatic modification

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J.* 2025;13(2):46–61.
DOI: 10.15406/emij.2025.13.00370

Table 2 Continued...

Process Regulation	Not a regulated process	A regulated process
Sugars Added	Glucose, fructose, or galactose are the sugars added	Glycans, mannose, xylose, fucose, etc., are the sugars added
Protein Maturity	Occurs in mature proteins	Occurs in immature or unmodified proteins
Effect on Functionality	Makes the protein non-functional	Makes the protein functional
Effect on Stability	Decreases the stability of the protein	Increases the stability of the protein

Reasons to prefer HbA1c Over Plasma glucose for diagnosing diabetes

Haemoglobin A1c offers several advantages over plasma glucose measurements, particularly fasting plasma glucose (FPG), for diagnosing and monitoring diabetes. One of its most significant strengths is that HbA1c reflects chronic hyperglycemia, capturing longer-term glycemic exposure that single or repeated FPG measurements may miss.[31] HbA1c is strongly associated with microvascular complications such as diabetic retinopathy, with evidence showing its predictive power is comparable to, if not greater than, that of FPG. Moreover, HbA1c correlates more reliably with cardiovascular disease (CVD) risk than FPG (9).

A practical advantage of the HbA1c test is that it does not require fasting, allowing for easier scheduling and greater patient compliance.[32] Unlike FPG, it is not influenced by acute physiological changes such as stress, recent dietary intake, physical exertion, or smoking.[9] HbA1c also boasts better pre-analytical stability, meaning it can withstand variations in sample handling or storage, and has analytical variability comparable to that of glucose assays.[33] Standardization efforts for HbA1c measurement are well-developed and comparable to those for glucose assays.[33]

Biologically, HbA1c is less variable than FPG and 2-hour plasma glucose (OGTT), with coefficients of variation (CV) of approximately 3.6% for HbA1c, 5.7% for FPG, and 16.6% for postprandial glucose (PPG). Additionally, HbA1c may detect individual variations in protein glycation propensity, which could indicate higher complication risks (e.g., as indexed by the Hemoglobin Glycation Index, HGI). Clinically, HbA1c can be used simultaneously for diagnosis and for initiating a long-term monitoring plan, making it a dual-purpose tool.[34,35]

Reasons not to prefer HbA1c Over plasma glucose for diagnosing diabetes

Despite its utility, HbA1c is not without limitations. Fundamentally, diabetes is defined by elevated blood glucose levels, not by the glycation of proteins. HbA1c may fail to detect key pathophysiological abnormalities of diabetes, and its sensitivity for diagnosing the disease is relatively poor. Using HbA1c as the sole diagnostic tool could significantly alter diabetes epidemiology.

The 2-hour plasma glucose level from an oral glucose tolerance test (OGTT) and impaired glucose tolerance (IGT) are both stronger predictors of cardiovascular disease than HbA1c. Approximately 40% of all-cause mortality occurs in individuals with IGT despite normal HbA1c levels. Fasting is also not strictly necessary for identifying metabolic disturbances, especially when using OGTT.

Moreover, the global standardization of HbA1c assays remains inconsistent, even in developed nations, while glucose assays are generally easier to harmonize. Ethnic variability in HbA1c results has also been observed and remains poorly understood. Within-day biological fluctuations in plasma glucose, such as those caused by diet, physical or mental activity, and sleep, may provide more insight into glucose metabolism than a single HbA1c value. Importantly, individual differences in hemoglobin glycation do not always reflect diabetic pathophysiology, which can limit the relevance of HbA1c in certain clinical scenarios.[34–36]

Limitations of HbA1c

Multiple physiological and pathological conditions can affect HbA1c levels independently of actual glycemia. These include disorders impacting erythrocyte lifespan or turnover, such as hemoglobinopathies, malaria, anemia, significant blood loss, chronic kidney disease (CKD), neonatal status, medication use, and pregnancy.[37,38] The correlation between HbA1c and fasting plasma glucose is moderate (~0.85), implying that about 30% of the variance in one is not explained by the other.[38]

Furthermore, little is known about the behaviour of HbA1c during the early stages of diabetes development. HbA1c levels in the 6.0–6.5% range do not predict diabetes onset as effectively as FPG or OGTT values. The sensitivity of HbA1c in detecting diabetes, particularly as defined by OGTT criteria, is under 50%, meaning that more than half of cases could go undetected if only HbA1c is used.[39]

The threshold values of HbA1c for predicting long-term complications such as retinopathy or nephropathy are also not established and may lie below the current diagnostic cut-off of 6.5%. Additionally, no major diabetes prevention trials have selected participants based solely on HbA1c values. Alarmingly, reliance on HbA1c alone could delay the diagnosis of up to 60% of new diabetes cases.

Alternative biomarkers to HbA1c

While HbA1c remains the most used biomarker for long-term glycemic control, several alternative markers offer valuable insights, particularly when HbA1c is unreliable due to various physiological or clinical conditions.

Fructosamine

Fructosamine is a ketoamine formed via the glycosylation of serum proteins, mainly albumin. It reflects mean blood glucose levels over the preceding 2 to 3 weeks, resulting in a shorter-term view compared to HbA1c.

Fructosamine assays are inexpensive and relatively simple to perform, making them a practical option in clinical settings. When combined with HbA1c and other glycemic indicators, fructosamine can help identify short-term fluctuations in blood glucose that might otherwise go unnoticed. However, the accuracy of fructosamine measurements can be compromised by conditions that alter albumin turnover or metabolism, such as nephrotic syndrome or hepatic dysfunction.[40]

Glycated Albumin (GA)

Glycated albumin (GA) is the ratio of glycated albumin to total albumin in the serum. Like fructosamine, GA reflects glycemic control over a 2–3-week period, but it offers the advantage of not being affected by total serum albumin concentrations. GA levels are typically three times higher than corresponding HbA1c values and are especially useful in patients with hematologic disorders (e.g., anemia, hemorrhage), pregnancy, liver cirrhosis, or neonatal diabetes. Furthermore, GA may be more responsive in situations where glycemia rapidly improves or deteriorates, such as in fulminant type 1 diabetes mellitus (T1DM). Still, GA measurements can be limited in the presence of abnormal albumin metabolism.[40]

1,5-Anhydroglucitol (1,5-AG)

1,5-Anhydroglucitol (1,5-AG) is a glucose-like molecule that competes with glucose for reabsorption in the kidneys. When serum glucose level surpasses approximately 180 mg/dL, 1,5-AG is competitively expelled in urine, resulting in a drop in serum 1,5-AG levels. As a result, low 1,5-AG levels reflect recent hyperglycemia and glycosuria over the past 1–2 weeks. This biomarker is particularly valuable for detecting postprandial glycemic excursions and may help evaluate glycemic variability in individuals with T1DM. However, its accuracy is influenced by renal function, making it less reliable in patients with altered renal hemodynamics.[40]

What is Time in Range (TIR)?

Time in Range (TIR) is described as the percentage of time a person with diabetes spends within a defined target glucose range. For most individuals, this range lies between 70 and 180 mg/dL (approximately 3.9–10.0 mmol/L). A TIR exceeding 70%, equivalent to about 17 hours out of a 24-hour period, is typically recommended as the therapeutic goal for glycemic control.[41–43]

Continuous glucose monitoring systems are the most precise and convenient tool for measuring TIR. These wearable devices calculate glucose levels in the interstitial fluid around the clock, giving a comprehensive picture of glycemic trends. Data from CGMs can be easily downloaded via software or mobile applications to generate TIR profiles for any chosen time window.[41,44]

While finger-prick capillary blood glucose checks can also be used to estimate TIR, achieving acceptable accuracy requires multiple measurements throughout the day (47). CGM has thus enabled more patients and their healthcare providers to use TIR as a practical and effective metric for diabetes management. By analyzing TIR, providers can set individualized goals and adjust treatment regimens more responsively.[41,45]

What does a TIR report look like?

Software programs for CGMs represent TIR information as a color-coded vertical bar. The bar will show the percentage of time you're in various ranges. Figure 3 The TIR section is usually green, while other ranges take on shades of yellow, orange, red, or dark red.[44] Below are the readings and their representations:

a) 70 to 180 mg/dL (TIR)

b) < 54 mg/dL — very low II (TBR)

c) 54 to 69 mg/dL — low I (TBR)

d) 181 to 250 mg/dL — high I (TAR)

e) 250 mg/dL — very high II (TAR)

What Should Your TIR Be?

The optimal TIR is not a one-size-fits-all target. Instead, it should be determined collaboratively between the patient and their healthcare provider, based on individual needs, health status, and treatment goals. While a general TIR target of greater than 70% is recommended for most individuals with diabetes, personalized targets are often necessary.[45]

Several clinical factors influence individualized glucose targets, including the duration of diabetes and the patient's age or overall life expectancy. Additionally, certain medical conditions, such as chronic kidney disease (CKD) or gastroparesis, may affect blood glucose regulation and warrant adjustments in TIR goals. Other considerations include the presence of established cardiovascular disease (CVD), hypoglycemia unawareness, and whether the patient is pregnant or planning for pregnancy. Tailoring TIR targets based on these variables ensures safer and more effective diabetes management across diverse patient populations (Figure 4).[45]

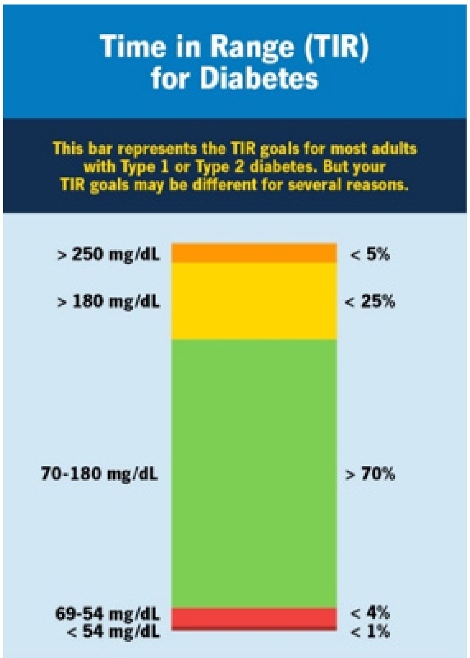

Figure 3 Time in Range (TIR) goals for diabetes management, courtesy of cleveland clinic.[41]

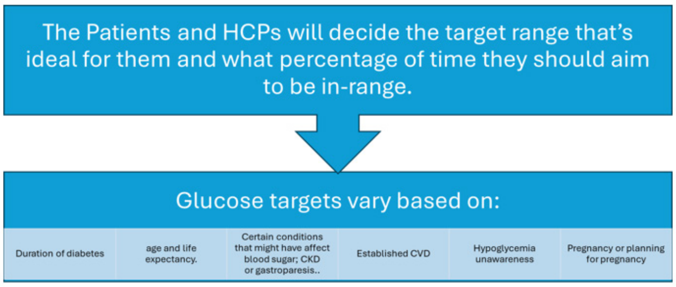

Figure 4 Individualization of Time in Range (TIR) targets.

CGM-based time in range (TIR) targets for adults with type 1 or type 2 diabetes

The utilization of continuous glucose monitoring (CGM) has enabled the development of standardized TIR targets for adults with diabetes. These targets vary depending on age, risk profile, and comorbid conditions, ensuring that glycemic goals remain both safe and achievable for diverse patient populations.

For adults over the age of 25 with either type 1 or type 2 diabetes, the recommended TIR, defined as the percentage of time glucose levels remain between 70 and 180 mg/dL, is greater than 70%. This benchmark equates to approximately 17 out of 24 hours each day spent within the target range and is associated with a reduced risk of both microvascular and macrovascular complications (Table 3).

DOI: 10.15406/emij.2025.13.00370

Table 3 CGM-Based Time in Range (TIR) Targets for Adults with Type 1 or Type 2 diabetes**,** recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42:1593–1603.[45]

CGM-derived metric	Adults (>25 Years) with Type 1 or Type 2 Diabetes	Older or High-Risk Adults with Type 1 or Type 2 Diabetes
TIR (70–180 mg/dL [3.9–10.0 mmol/L])	>70% of CGM readings or >16 hours, 48 minutes per day	>50% of CGM readings or >12 hours per day
TBR Level 1 (<70 mg/dL [3.9 mmol/L])	<4% of CGM readings or <1 hour per day	<19% of CGM readings or <15 minutes per day
TBR Level 2 (<54 mg/dL [3.0 mmol/L])	<1% of CGM readings or <15 minutes per day	<1% of CGM readings or <15 minutes per day
TAR Level 1 (>180 mg/dL [10.0 mmol/L])	<25% of CGM readings or <6 hours per day	<50% of CGM readings or <12 hours per day
TAR Level 2 (>250 mg/dL [13.9 mmol/L])	<5% of CGM readings or <1 hour, 12 minutes per day	<10% of CGM readings or <2 hours, 24 minutes per day

For older adults or those classified as high-risk, including individuals with advanced complications or significant comorbidities, a more relaxed TIR target of greater than 50% is considered appropriate. This adjustment allows for safer glycemic control by minimizing the risk of hypoglycemia, particularly in populations with greater clinical vulnerability.

These tailored targets reflect international consensus recommendations and are intended to support individualized diabetes care that balances efficacy with patient safety.[45]

TIR targets for adults with type 1 diabetes during pregnancy

According to the International Consensus on Time in Range, published in Diabetes Care.,[46] specific TIR goals have been established for adults with type 1 diabetes during pregnancy to optimize maternal and fetal outcomes. The recommended targets include spending at least 70% of the time with glucose levels between 63 and 140 mg/dL, which is considered the ideal in-range zone for pregnancy. In addition, time spent below 63 mg/dL should be limited to less than 4%, reducing the risk of hypoglycemia-related complications. Similarly, time spent above 140 mg/dL should not exceed 25%, aiming to prevent hyperglycemia and associated adverse outcomes (Figure 5).

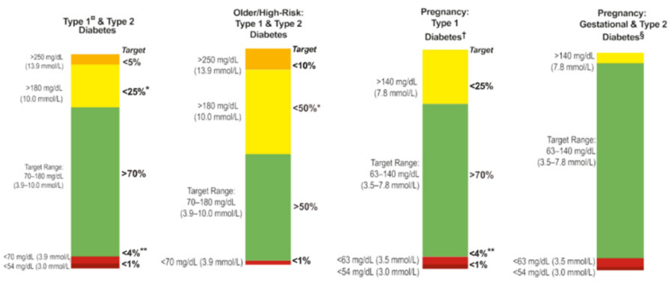

Figure 5 CGM-based glucose targets across diverse diabetes populations, courtesy of the international consensus on time in range.[45]

While these recommendations are well-supported for type 1 diabetes in pregnancy, it is important to note that the evidence for CGM use in type 2 diabetes (T2DM) during pregnancy and in gestational diabetes mellitus (GDM) remains limited. To date, no randomized controlled trials (RCTs) have specifically evaluated CGM effectiveness in these populations. Consequently, clinical guidance for CGM in T2DM and GDM during pregnancy is currently based on extrapolated data and expert opinion rather than robust clinical trial evidence.[45]

CGM-based glucose targets for specific diabetes populations

Continuous glucose monitoring (CGM) allows for tailored glycemic targets across different patient populations with diabetes. These targets aim to optimize glycemic control while minimizing the risk of hypoglycemia, especially in vulnerable groups such as children, older adults, and pregnant women.

For individuals under the age of 25, when the HbA1c goal is set at 7.5%, the corresponding Time in Range (TIR) target should be approximately 60%. This recommendation supports the unique challenges in pediatric and adolescent diabetes management, though further clinical research is required to validate and refine these benchmarks.

The percentage of time in specific glucose ranges, such as below 54 mg/dL or above 250 mg/dL, has been included in the recommendations but is based on limited evidence. Therefore, these values should be interpreted cautiously until more robust data becomes available.

In pregnant individuals, particularly those with type 1 diabetes or gestational/type 2 diabetes, specific CGM targets have been proposed but not yet universally finalized due to a lack of extensive clinical trial data. Clinicians are encouraged to refer to pregnancy-specific sections in current guidelines to adjust targets accordingly.

Key parameters in the CGM-based profiles include:

a. Very high glucose (≥250 mg/dL or 13.9 mmol/L)

b. Very low glucose (<54 mg/dL or 3.0 mmol/L)

Ongoing studies are expected to provide more conclusive guidance, especially for populations where CGM use has not been thoroughly evaluated, such as younger patients and pregnant women with type 2 diabetes or gestational diabetes. For now, CGM data should be used in conjunction with individualized clinical judgment to set safe and achievable goals.[45]

The relationship between HbA1c and Time in Range (TIR)

Time in Range (TIR) and HbA1c are both valuable metrics in the assessment of glycemic control, but they capture different aspects of glucose dynamics. TIR measures the proportion of time an individual's glucose levels remain within a target range, typically over hours to days, depending on how long and consistently a continuous glucose monitor (CGM) is used. In contrast, HbA1c reflects the average glucose levels over the past two to three months, providing a retrospective overview of glycemic exposure.

One of the key distinctions is that HbA1c does not offer insights into blood sugar variability or fluctuations throughout the day. TIR fills this gap by capturing real-time patterns and daily glucose excursions. Research has demonstrated a clear inverse linear relationship between TIR and HbA1c. Specifically, a TIR of approximately 70% corresponds to an HbA1c of about 6.5–7.0%, and each 10% increase in TIR typically aligns with an approximate reduction of 0.8% in HbA1c.

A useful analogy compares HbA1c to reading a chapter summary of a book; it provides the overall picture but lacks detail. In contrast,

DOI: 10.15406/emij.2025.13.00370

CGM and TIR offer the full narrative, allowing both healthcare professionals and patients to understand the daily variations and challenges of glucose control more precisely. While HbA1c has been the clinical standard since the 1960s, the advent of CGM technology has made TIR a more nuanced and actionable measure of diabetes management.[45]

TIR and the role of CGM

Continuous glucose monitoring (CGM) is the most precise method for assessing TIR. These disposable, wearable medical devices track blood glucose levels around the clock. A small sensor inserted under the skin measures glucose concentrations in the interstitial fluid every few minutes. The data are then transmitted to a connected display, either a dedicated receiver or a smartphone application, allowing for real-time monitoring.

Some insulin pumps now feature integrated CGM functionality, enabling automated insulin delivery based on real-time glucose data. This enhances the precision of glycemic management, especially in individuals with frequent fluctuations or poor control. Based on CGM data, patients and clinicians can obtain a virtually continuous readout of glucose trends, offering insights that static blood glucose tests simply cannot provide.

CGMs are particularly recommended for people with type 1 or type 2 diabetes who have trouble achieving stable glucose control, especially those with complications such as diabetic retinopathy, obesity, or chronic kidney disease (CKD). Individuals with insulin-dependent diabetes mellitus (IDDM) also greatly benefit from CGM-based insights.[47]

TIR guidelines and recommended glucose ranges

Time in Range recommendations vary based on individual characteristics, but an international consensus, led by the American Diabetes Association (ADA) and other global organizations, has helped establish standardized glucose targets. In general, the recommended fasting glucose range is between 4.2 and 5.4 mmol/L (approximately 75.6 to 97.2 mg/dL), while the target postprandial (2-hour) glucose should not surpass 7.8 mmol/L (around 140.4 mg/dL).[48–50]

These ranges are the result of multiple clinical trials aiming to determine which glucose thresholds are associated with the lowest risk for both acute and long-term complications. While these benchmarks offer a strong starting point, continued collaboration with healthcare providers is essential to tailor the exact targets based on individual patient profiles and clinical context.

How to measure TIR?

TIR can be measured using two primary methods. The most accurate and comprehensive approach is through CGM systems, with Dexcom currently leading the market, alongside other manufacturers such as Abbott, Tandem, Medtronic, and Roche. CGMs continuously collect glucose data, offering real-time analysis and historical trend reporting.[50,51]

Alternatively, TIR can be estimated through manual fingerstick testing conducted several times a day. Although this method lacks the real-time and continuous nature of CGM, it can still provide meaningful data when readings are taken before and after meals, physical activity, and sleep. This approach helps build a clearer picture of how daily behaviours and activities impact blood glucose variability.[52,41]

Types of CGM devices

There are multiple types of CGM devices available to accommodate different clinical and lifestyle needs. These include:

a) **Real-time CGM (rtCGM):** Offers continuous glucose readings with automatic alerts for hypo- and hyperglycemia.[53]

b) **Intermittently scanned CGM (isCGM):** Requires the user to scan the sensor to obtain glucose data.[53]

c) **Hybrid closed-loop systems:** Integrate CGM with insulin delivery systems for automated glucose management.[54]

Each CGM system comprises three core components: a small subcutaneous sensor, a transmitter, and a display interface (either a standalone receiver or smartphone app) (Figure 6).[52,55]

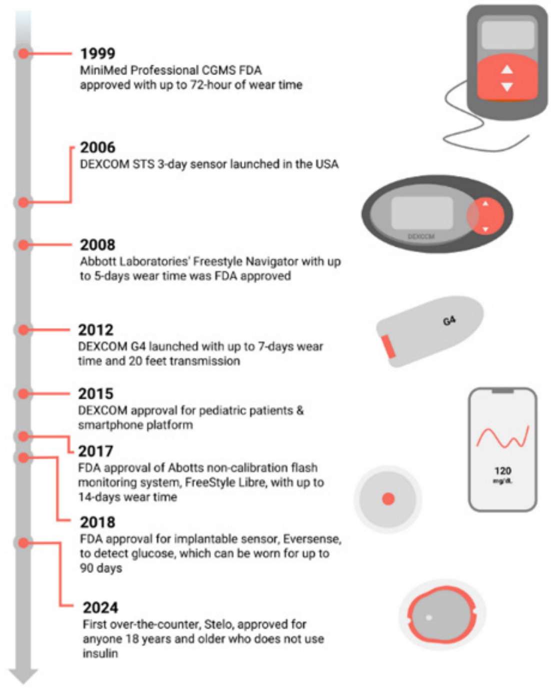

Figure 6 Timeline of Continuous Glucose Monitoring (CGM) device evolution, courtesy of Bender C, et al.,[55]

For optimal performance are references to support your summary of continuous glucose monitoring (CGM) device types and components:

This timeline outlines major milestones in the development and approval of CGM technologies from 1999 to 2024. Starting with the FDA approval of the MiniMed Professional CGMS in 1999, the timeline highlights innovations such as the launch of the DEXCOM G4 with extended wear time and mobile connectivity, Abbott's FreeStyle Libre as a non-calibration flash system, and Eversense, the first implantable CGM. The most recent advancement in 2024 is the approval of the first over-the-counter CGM, Stelo, for adults not using insulin.

Figure 7 This Figureure shows the various uses of CGM technology in diabetes management. Beyond real-time glucose tracking, CGMs support predictive modelling, early diagnostics, patient education, insulin dosing, and integration into Automated Insulin Delivery (AID) systems. They also play a critical role in clinical research and enable personalized treatment strategies, enhancing both short- and long-term outcomes for individuals with diabetes (Figure 7).

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J.* 2025;13(2):46‒61.
DOI: 10.15406/emij.2025.13.00370

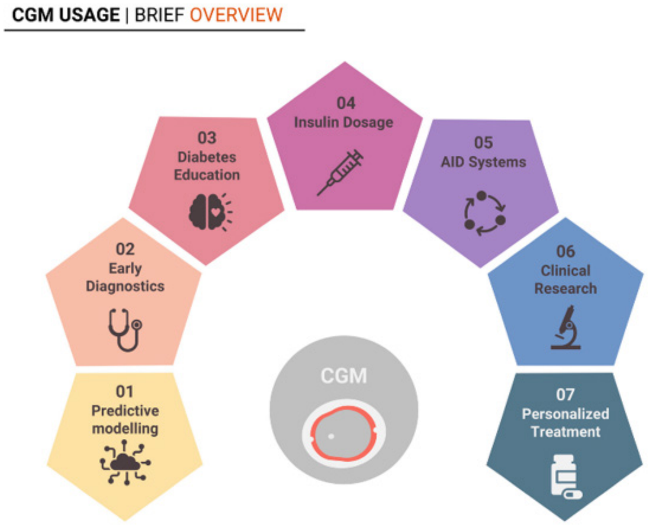

Figure 7 Overview of CGM applications in diabetes care, courtesy of Bender C, et. al.[55]

Why is TIR important?

TIR provides a more nuanced and dynamic understanding of glycemic control compared to traditional markers like HbA1c. Unlike HbA1c, which provides an average over several months, TIR reflects daily fluctuations, allowing clinicians and patients to visualize the true variability in glucose levels. These fluctuations are affected by numerous factors, including dietary intake, physical activity, medications, psychological stress, and acute illnesses.

Analysing TIR data through continuous glucose monitoring (CGM) provides actionable insights into how these daily factors impact glucose control. For instance, an individual may observe a significant reduction in their TIR during a period of illness, such as the flu. Recognizing such patterns enables patients to work with their healthcare providers to develop proactive management strategies for future events that may disrupt glycemic stability.[53]

Clinical rationale for TIR and CGM metrics

CGM-derived TIR and associated metrics provide actionable insights into glycemic control that go beyond what HbA1c alone can offer. Modern CGM systems not only monitor glucose in real-time but also provide predictive data that can be analysed in several formats, such as the percentage of readings within range, total hours spent in range per day, or both.

Three core metrics form the foundation for CGM-based glycemic assessments:

a) **Time in Range (TIR):** 70–180 mg/dL (3.9–10.0 mmol/L)

b) **Time Below Range (TBR):** <70 mg/dL (3.9 mmol/L), especially <54 mg/dL (3.0 mmol/L)

c) **Time Above Range (TAR):** >180 mg/dL (10.0 mmol/L), especially >250 mg/dL (13.9 mmol/L)

A landmark multicentre prospective study involving 153 non-diabetic individuals found that participants spent 96% of their time in the 70–140 mg/dL (3.9–7.8 mmol/L) range, which is now widely accepted as the normal range in non-diabetic individuals. This reference range offers a benchmark against which TIR in diabetes can be evaluated.

Glycemic variability

Glycemic variability refers to the amplitude, frequency, and duration of fluctuations in blood glucose levels. It is increasingly recognized as an independent risk factor for both hypoglycemia and hyperglycemia-related complications. The degree of variability is described as the coefficient of variation (CV), which is the standard deviation divided by the mean glucose level, multiplied by 100. A CV exceeding 36% is considered high and is associated with an increased risk of hypoglycemia.[53]

Another relevant CGM-derived metric is the Glucose Management Indicator (GMI), which estimates average glucose based on CGM data, assuming at least 70% active use over a 14-day period.

TIR and diabetes-related complications: Ongoing research

Emerging studies highlight the clinical significance of TIR in reducing the risk of both acute and chronic diabetes complications. High glycemic variability has been linked to oxidative stress and systemic inflammation, both of which exacerbate diabetic pathophysiology.

Specifically, increased glucose fluctuations have been associated with:

I. A higher incidence of hypoglycemic episodes

II. Elevated cardiovascular disease (CVD) risk

III. Decline in cognitive function

IV. Reduced quality of life (QOL)

V. Microvascular complications such as diabetic retinopathy and neuropathy, particularly cardiovascular autonomic neuropathy

These findings underscore the importance of incorporating TIR and glycemic variability metrics into routine diabetes care to improve patient outcomes and enable timely, personalized interventions (Figure 8).[40]

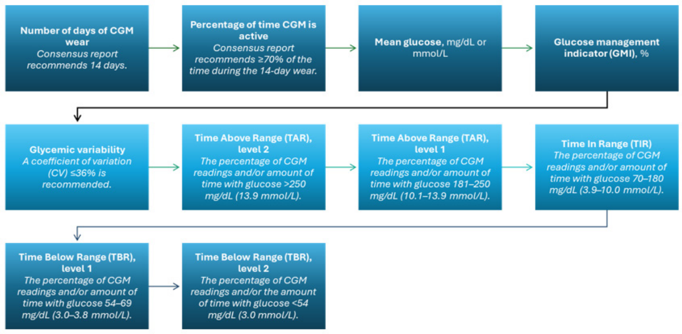

Figure 8 Standardized core metrics for Continuous Glucose Monitoring (CGM), courtesy of international consensus on time in range.[45]

Standardized Core CGM metrics

To ensure consistency and clinical utility in evaluating glycemic control using continuous glucose monitoring (CGM), a set of standardized core metrics has been established by expert consensus. These metrics are designed to comprehensively assess glucose trends, variability, and control in individuals with diabetes over a standardized monitoring period.

1) **Number of days of CGM wear**

The consensus recommendation is for at least 14 days of CGM data collection to ensure adequate representation of typical glucose patterns.

2) **Percentage of time CGM is active**

To be considered reliable, CGM devices should be active for at least 70% of the monitoring period, i.e., 10 out of the 14 days.

3) **Mean glucose**

The average glucose level over the wear period is calculated in either mg/dL or mmol/L, providing an overview of the individual's general glycemic exposure.

4) **Glucose Management Indicator (GMI)**

GMI is derived from mean CGM glucose values and estimates what the corresponding HbA1c value would be. This metric helps clinicians compare real-time glucose data to laboratory-based long-term markers.

5) **Glycemic variability (Coefficient of variation, CV%)**

The coefficient of variation (CV) is calculated as the standard deviation divided by the mean glucose level (multiplied by 100), is used to evaluate glycemic variability. A CV of ≤ 36% is considered optimal and indicates more stable glucose levels with reduced risk of hypoglycemia.

6) **Time in Range (TIR)**

TIR refers to the **percentage of time** glucose values are within the recommended target range of 70–180 mg/dL (3.9–10.0 mmol/L). Higher TIR is associated with reduced risks of diabetes-related complications.

7) **Time Above Range (TAR)**

TAR Level 1: Time spent with glucose between 181–250 mg/dL (10.1–13.9 mmol/L)

TAR Level 2: Time spent with glucose >250 mg/dL (13.9 mmol/L)

These metrics quantify the extent and severity of hyperglycemia.

8) **Time Below Range (TBR)**

TBR Level 1: Time with glucose between 54–69 mg/dL (3.0–3.8 mmol/L)

TBR Level 2: Time with glucose <54 mg/dL (3.0 mmol/L) These values reflect hypoglycemic risk and are particularly important for adjusting treatment in patients prone to low glucose episodes.

Collectively, these metrics provide a comprehensive, standardized framework for interpreting CGM data, enabling both clinicians and patients to make informed decisions aimed at optimizing glycemic control and minimizing complications.[45]

Evidence supporting Time in Range (TIR) as a predictor of diabetes complication risks

A growing body of evidence highlights **TIR**, as measured by continuous glucose monitoring (CGM) or structured glucose testing, as a significant clinical marker associated with the risk of diabetes-related complications, independent of HbA1c.

1) **Retinopathy and microalbuminuria (DCCT retrospective analysis)**

In a pivotal validation study by Beck et al., TIR derived from seven-point quarterly blood glucose profiles demonstrated a strong association with the risk of developing or progressing diabetic retinopathy and microalbuminuria. Importantly, this relationship remained significant even when controlling for HbA1c levels. These findings suggest that TIR can provide predictive value beyond what is captured by HbA1c alone in assessing microvascular risk in patients with diabetes.[56]

2) **Peripheral neuropathy and microvascular burden (CANDY Study)**

The CANDY study, involving 105 individuals with type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and diabetic polyneuropathy (DPN), revealed that lower TIR was independently associated with a higher prevalence of DPN. Specifically, each 10% reduction in TIR was linked to a 25% increased risk of developing DPN, regardless of HbA1c. The study emphasized that hyperglycemia and glycemic variability, as reflected by TIR, are key contributors to the overall burden of microvascular complications.[57]

3) **Carotid Intima-Media Thickness (CIMT) and cardiovascular risk**

A study by Lu et al. demonstrated that lower TIR was significantly associated with increased carotid intima-media thickness (CIMT), a surrogate marker for atherosclerosis and cardiovascular risk. Participants with abnormal CIMT had lower TIR, higher HbA1c, and increased glycemic variability. Notably, each 10% increase in TIR corresponded to a 6.4% reduction in the risk of abnormal CIMT, underscoring the vascular protective effect of maintaining optimal glucose range.[58]

4) **All-cause and cardiovascular mortality**

In a prospective cohort study, Lu et al. explored the relationship between TIR and mortality outcomes in patients with type 2 diabetes. The study concluded an inverse association between TIR and both all-cause and cardiovascular mortality. Specifically, for each 10% decrease in TIR, the hazard ratio (HR) for all-cause mortality increased by 1.08 (95% CI: 1.05–1.12), and for cardiovascular mortality, the HR increased by 1.05 (95% CI: 1.00–1.11). These findings suggest that reduced TIR is a significant predictor of adverse survival outcomes in individuals with diabetes (Figure 9).[57]

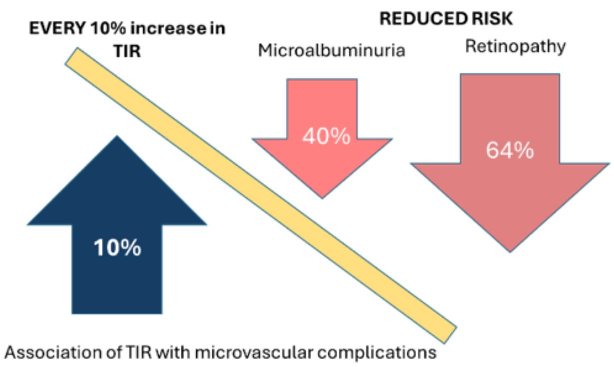

Figure 9 Impact of increased Time in Range (TIR) on microvascular complication risk.[56]

Time in Range (TIR) and risk reduction in microangiopathy

Evidence consistently supports a strong inverse relationship between TIR and the risk of microvascular complications in individuals

DOI: 10.15406/emij.2025.13.00370

with diabetes. Increasing TIR is associated with substantial reductions in the prevalence and progression of key microangiopathic outcomes, including retinopathy and microalbuminuria.

For every 10% increase in TIR, studies have shown:

I. A 40% reduction in the risk of developing or worsening diabetic retinopathy

II. A 64% reduction in the risk of microalbuminuria, a key early indicator of diabetic kidney disease

These findings emphasize the critical importance of maintaining glucose levels within the target range (70–180 mg/dL) as a preventive strategy against long-term microvascular damage. TIR serves not only as a snapshot of current glycemic control but also as a powerful predictor of future diabetes complications, reinforcing its value in routine clinical practice (Table 4).[58]

Table 4 Association between Time in Range (TIR) and all-cause mortality, data adapted from: Lu J, Wang C et al.,[58]

Time-in-Range	Hazard ratios for all-cause mortality
TIR > 85%	1
TIR 71-85%	1.23
TIR 51-70%	1.3
TIR ≤ 50%	1.83

Comparison of hazard ratio for all-cause mortality, based on glucose TIR

This table presents hazard ratios for all-cause mortality based on glucose Time in Range (TIR). Individuals with TIR more than 85% serve as the reference group (HR = 1.00). As TIR decreases, the risk of mortality increases significantly:

1) TIR 71–85%: HR = 1.23

2) TIR 51–70%: HR = 1.30

3) TIR ≤50%: HR = 1.83

These findings underscore the prognostic importance of maintaining higher TIR in individuals with diabetes, linking better glycemic control with lower mortality risk.

Example of daily glucose patterns: Taken from daily life

AGP case report 1

This case involves a 67-year-old male patient diagnosed with type 2 diabetes mellitus. His medical history is significant for morbid obesity (BMI: 40), dyslipidemia, hypertension, and obstructive sleep apnea (OSA), factors that compound cardiovascular and metabolic risk. The patient is on a pharmacologic regimen consisting of metformin and once-weekly dulaglutide, a GLP-1 receptor agonist known for its benefits in glycemic control and weight management. The clinical concern at presentation was a recent rise in glycated hemoglobin (A1C) from 6.5% to 7.6%, which the patient attributed to dietary indiscretions during the holiday season (Table 5).

To evaluate the underlying glycemic trends more accurately, a continuous glucose monitoring (CGM) system was used over 15 days, from March 2 to March 16, 2020. The patient maintained 100% CGM wear time, ensuring high data reliability.

The CGM data revealed an average glucose level of 149 mg/dL, corresponding to a Glucose Management Indicator (GMI) of 6.9%, which is significantly lower than the lab-reported A1C of 7.6%. This discrepancy suggests that the A1C elevation may be transient or influenced by factors such as red blood cell turnover or recent glycemic excursions not representative of long-term trends (Figure 10).

Table 5 Target glucose ranges and Daily Time-in-Range (TIR) Goals for Type 1 or Type 2 diabetes – case 1.

Ranges and targets for	Type 1 or Type 2 diabetes	Targets % of readings (Time/Day)
Glucose ranges	Target Range 70–180 mg/dL	>70% (21h 22min)
	Below 70 mg/dL	<4% (58min)
	Below 54 mg/dL	<1% (14min)
	Above 180 mg/dL	<5% (58min)
	Above 250 mg/dL	≤1% (14min)

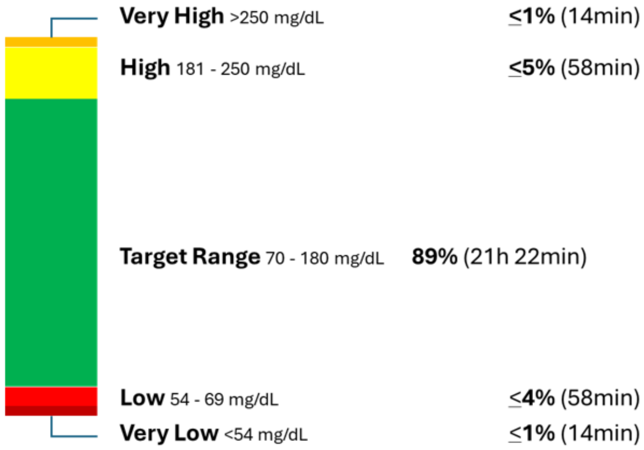

Figure 10 Time-in-Range (TIR) distribution – AGP case report 1.

A key strength of this patient's glucose control can be seen in his Time in Range (TIR; 70–180 mg/dL), which was 89%, a higher rate than the international consensus target of >70% for most adults with diabetes. This level of TIR translates to approximately 21 hours and 20 minutes per day spent within the optimal glucose range, indicating excellent daily glycemic control. Importantly, Time Below Range (TBR), which includes levels <70 mg/dL and especially <54 mg/dL, associated with increased hypoglycemia risk, was 0%, demonstrating complete avoidance of hypoglycemic episodes. This is particularly reassuring in older patients, where hypoglycemia can be associated with falls, cardiovascular events, and cognitive impairment.

Time above Range (TAR; >180 mg/dL) was modest at 6%, suggesting infrequent postprandial hyperglycemia or other transient glucose elevations. Given that the clinical target for TAR is to remain under 25%, this patient's result indicates strong overall control. Furthermore, glucose variability, measured as the coefficient of variation (CV), was 15.2%, far below the consensus threshold of 36%. Low variability is an important marker of metabolic stability and is associated with a reduced risk of complications and improved quality of life (Figure 11).[40]

Time in Ranges: AGP case report 1

The distribution of glucose values over a 24-hour period provides critical insights into glycemic control. In this AGP profile, color-coded segments illustrate the percentage of time spent in various glucose ranges during the 15-day CGM wear period:

a) **Very High (>250 mg/dL):** <1% (approximately 14 minutes/day)

b) **High (181–250 mg/dL):** <5% (approximately 58 minutes/day)

c) **Target Range (70–180 mg/dL): 89%** (approximately 21 hours and 22 minutes/day)

d) **Low (54–69 mg/dL):** <4% (approximately 58 minutes/day)

e) **Very Low (<54 mg/dL):** <1% (approximately 14 minutes/day)

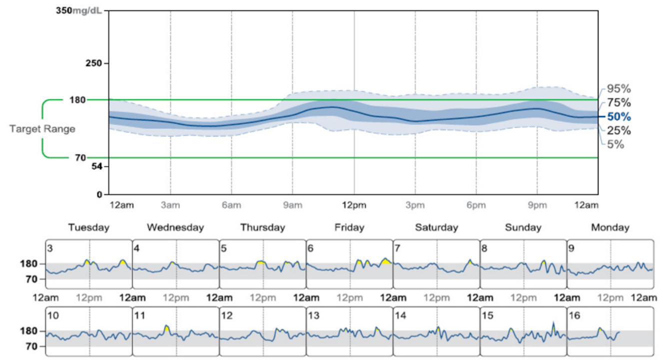

Figure 11 Ambulatory Glucose Profile (AGP) and daily glucose trends – case report 1.

Source: Battelino, Tadej, et al.[45]

This distribution reflects excellent glycemic control, with the patient spending most of the time within the recommended target range. Minimal time is spent in both hypoglycemic and hyperglycemic zones, indicating stable glucose regulation. TIR of 89% far exceeds the consensus benchmark of >70%, suggesting reduced risk for both acute and chronic complications. This case exemplifies how TIR and related CGM metrics can be used effectively to evaluate and guide diabetes management.

The Ambulatory Glucose Profile (AGP) curve has shown mild and brief elevations in glucose during the mid-morning and evening hours, likely linked to meals. However, these excursions remained within safe parameters and did not contribute significantly to TAR or affect the overall glycemic profile.

Ambulatory Glucose Profile (AGP): Case 1

The Ambulatory Glucose Profile (AGP) is a standardized graphical representation of glucose trends over a selected monitoring period. It combines multiple days of CGM data into a single 24-hour curve, showing the median (50%), interquartile range (25%–75%), and interdecile range (5%–95%). This summary visualizes overall glucose control and variability across typical days, aiding in the identification of patterns that may not be obvious through average values alone.

The accompanying daily glucose profiles (March 3–16) show day-by-day glucose fluctuations. These plots allow clinicians to correlate specific trends with patient behaviours, such as meal timing, physical activity, or medication adherence.[45]

Case 1 summary

1) **Patient Profile:** A 67-year-old male with type 2 diabetes, obesity (BMI: 40), and comorbid conditions including dyslipidemia, hypertension, and obstructive sleep apnea (OSA).

2) **Medication Regimen:** Metformin and weekly dulaglutide.

3) **Clinical Concern:** A recent rise in HbA1c from 6.5% to 7.6%, reportedly attributed to increased caloric intake during the holiday season.

CGM Results (15-Day Review):

a) **Time in Range (TIR, 70–180 mg/dL):** 89% — significantly above the recommended >70%, indicating excellent glycemic control.

b) **Time Below Range (TBR):** 0% — no hypoglycemia observed.

c) **Time Above Range (TAR):** 6% — within acceptable limits.

d) **Glucose Management Indicator (GMI):** 6.9% — lower than the lab-reported A1C, suggesting recent glucose control has been better than reflected by A1C.

e) **Glycemic Variability (GV, %CV):** 15.2% — well below the clinical concern threshold of 36%, indicating stable blood glucose levels.

Interpretation

Despite the concerning rise in A1C, CGM data strongly suggest that this patient has excellent and stable glycemic control. The GMI, TIR, and GV all support this conclusion, and the absence of both hypoglycemia and sustained hyperglycemia reinforces the effectiveness of the current treatment regimen. The mild discrepancy between A1C and GMI may be due to temporary dietary variations, laboratory measurement variability, or biological factors unrelated to day-to-day glucose control.

Action plan

Given the strong metrics from CGM, no immediate pharmacologic changes are recommended. Continued monitoring is advised, with a focus on refining dietary intake during mid-morning and evening periods to minimize postprandial glucose peaks. This case exemplifies how CGM can provide a comprehensive, nuanced assessment of glycemic control that may not be captured by A1C alone, enabling more personalized and precise diabetes management.

AGP report – Case 2 (February 19 – March 4, 2020)

This case involves a 73-year-old male patient with type 2 diabetes mellitus and a complex medical history that includes stage 4 chronic kidney disease (eGFR: 19 mL/min/1.73 m²), obesity (BMI: 33), and gout. The patient is treated with a fixed-dose insulin regimen consisting of a premixed 70/30 NPH/regular insulin combination, administered as 50 units both in the morning and evening, with an additional 10 units at larger meals. At initial assessment, his laboratory A1C had decreased markedly from 12.3% to 9.0%, prompting an initial impression of therapeutic improvement. However, due to the high cardiovascular and hypoglycemia risk in this patient population, particularly those with renal impairment, a more granular assessment using continuous glucose monitoring (CGM) was warranted (Figure 12).

Ranges And Targets For	Type 1 or Type 2 Diabetes	Targets % of Readings (Time/Day)
Glucose Ranges	Target Range 70–180 mg/dL	>50% (12h 57min)
	Below 70 mg/dL	≤5% (1h 12min)
	Below 54 mg/dL	≤14% (3h 22min
	Above 180 mg/dL	≤20% (4h 48min)
	Above 250 mg/dL	≤7% (1h 41min)

Figure 12 Target glucose ranges and Daily Time-in-Range (TIR) Goals for Type 1 or Type 2 diabetes – case 2.

The patient wore the CGM device continuously from February 19 to March 4, 2020, ensuring 100% data capture over the 15 days. Despite an average glucose of 141 mg/dL, which corresponds to a

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J.* 2025;13(2):46‒61.
DOI: 10.15406/emij.2025.13.00370

Glucose Management Indicator (GMI) of 6.7%, the deeper insights provided by CGM told a different story. The patient's Time in Range (TIR; 70–180 mg/dL) was just at 54%, significantly lower than the recommended clinical target of >70%. This means that for nearly 11 out of every 24 hours, the patient's glucose levels were outside the safe range.

Most concerning was the Time below Range (TBR), which stood at a critically high 19%, including 14% in Level 2 hypoglycemia (<54 mg/dL). This equates to nearly 4.5 hours per day spent in hypoglycemia, far exceeding the safe limit of <1% for Level 2 lows. Such prolonged and repeated episodes of hypoglycemia are particularly dangerous in elderly patients with renal dysfunction, as they can precipitate cardiac arrhythmias, cognitive impairment, and falls, and may go unrecognized due to impaired hypoglycemia awareness (Figure 13).

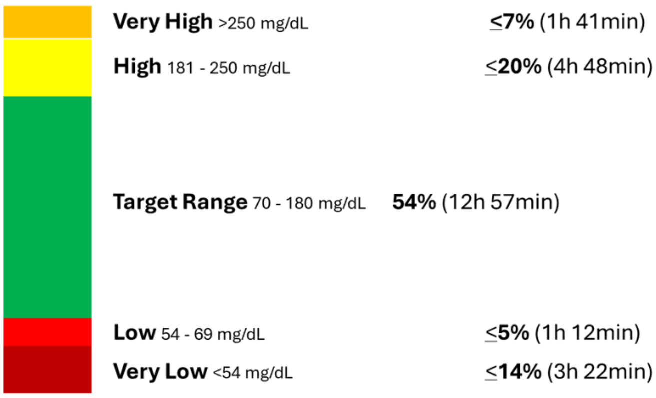

Figure 13 Time-in-Range (TIR) distribution – AGP case report 2.

The Time above Range (TAR) was 27%, which approaches the upper limit of acceptability (target <25%). These excursions likely reflect postprandial spikes and contribute to the overall glycemic instability. This is further supported by the patient's glucose variability (GV), which was a striking 54.5%, well above the recommended threshold of ≤36%. Such a high coefficient of variation (CV) indicates extreme fluctuations in glucose levels, a pattern associated with increased risks of both microvascular and macrovascular complications, and poor quality of life.

While the GMI of 6.7% might suggest good glycemic control at first glance, it is misleading in this context. The GMI is a weighted average of glucose readings and does not represent variability or frequency of hypoglycemia. The discrepancy between this patient's improved A1C and the CGM metrics underscores a major limitation of A1C: it can mask dangerously unstable glucose patterns, particularly in individuals with impaired renal function, where red blood cell turnover and azotemia can alter A1C readings.

Time in Ranges – Case 2 overview

The **Time in Range (TIR)** chart for Case 2 shows a comprehensive distribution of glucose levels across multiple glycemic ranges over a 15-day period. These categories, displayed as color-coded segments, offer valuable insight into the overall quality of glucose control and risk stratification for diabetes-related complications.

a) **Target Range (70–180 mg/dL)** – *Green*: The patient spent 55% of the time within the recommended target range, which indicates a moderate level of glycemic control. While this is above the 50% threshold, there remains room for improvement to reduce variability and enhance outcomes.

b) **Time above Range (181–250 mg/dL)** – *Yellow*: The patient experienced 21% of the time in this mildly elevated range, suggesting some postprandial or random hyperglycemic excursions that may require closer dietary or medication review.

c) **Time above 250 mg/dL** – *Orange*: 7% of the readings were in this significantly elevated hyperglycemic zone. Time in this range should ideally be minimized, as prolonged exposure to such levels increases the risk of long-term complications.

d) **Time below Range (54–69 mg/dL)** – *Red*: 7% of the time was spent in the Level 1 hypoglycemia range. Although mild, this still warrants attention, especially if recurrent or symptomatic.

e) **Time below 54 mg/dL** – *Dark Red*: A concerning 10% of readings fell into the Level 2 hypoglycemia range, which is considered clinically significant and potentially dangerous. This high frequency of severe hypoglycemia is alarming and necessitates immediate intervention to mitigate risks such as cognitive impairment, cardiovascular events, or loss of consciousness (Figure 14).

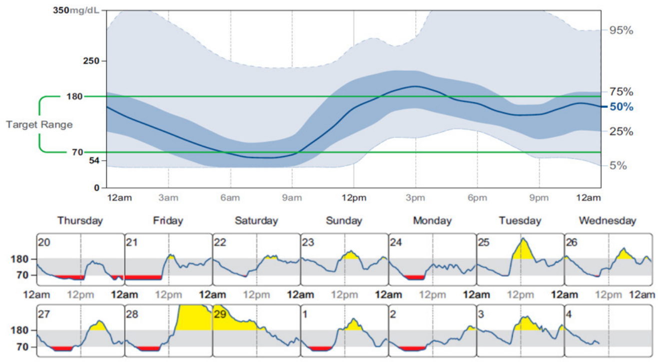

Figure 14 Ambulatory Glucose Profile (AGP) and daily glucose trends – case report 2.[40]

The **Ambulatory Glucose Profile (AGP)** showed clear patterns of severe early-morning hypoglycemia, likely caused by excessive evening insulin dosing, and afternoon hyperglycemia, potentially linked to high carbohydrate intake or insufficient prandial insulin adjustments. These opposing extremes on the glucose curve illustrate the challenges of managing diabetes with a rigid, premixed insulin regimen in patients with reduced renal clearance and high insulin sensitivity variability.[45]

Case 2 summary

1) **Patient profile**: 73-year-old man with type 2 diabetes, CKD stage 4 (eGFR 19), obesity (BMI 33), and gout.

2) **Medications**: Mixed NPH/regular insulin 70/30, 50 units AM/PM + 10 units for larger meals.

3) **Issue**: A1C decreased dramatically from 12.3% to 9%.

4) **CGM results**:

a. **TIR**: 54% (below goal)

b. **TBR**: 19% (very high; 14% in level 2 hypoglycemia)

c. **TAR**: 27% (borderline)

d. **GMI**: 6.7% (seems better than A1C)

e. **GV**: 54.5% (very high variability)

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J.* 2025;13(2):46–61.
DOI: 10.15406/emij.2025.13.00370

Clinical interpretation: Despite a significant reduction in A1C, this patient's glycemic control remains highly unstable and unsafe. The elevated TBR and extreme GV place him at significant risk for hypoglycemic complications, particularly in the context of advanced CKD. The GMI is not a reliable representation of clinical stability in this case. This highlights the importance of using CGM data in conjunction with traditional metrics to accurately evaluate glucose control.

Action plan: Immediate adjustments to the insulin regimen are warranted. The evening insulin dose should be reduced to mitigate nocturnal hypoglycemia, while the morning dose may be maintained. Additionally, dietary counselling should focus on moderating carbohydrate intake during breakfast to address the postprandial hyperglycemia pattern. Consideration should also be given to transitioning the patient to a basal-bolus insulin regimen or incorporating a GLP-1 receptor agonist (if not contraindicated) to allow for greater flexibility and reduced risk of hypoglycemia. Ongoing CGM monitoring is recommended to ensure stabilization and safe titration.

This case highlights how apparent improvements in A1C can mask life-threatening glycemic instability and underscores the invaluable role of CGM metrics in guiding safe and effective diabetes management, particularly in high-risk populations.[45]

Suggested studies that integrate the evaluation of the comparison between TIR and HbA1C

The integration of these studies adds depth and clinical relevance to our research

A recent review by Goshrani et al.,[59] further reinforces the evolving paradigm that positions Time in Range (TIR) as a critical metric in diabetes management, particularly in T2 diabetes research. Their work systematically compares TIR with HbA1c across clinical, physiological, and technological dimensions, and echoes several of the conclusions reached in this article. Notably, they highlight that TIR demonstrates stronger correlations with microvascular complications such as retinopathy, nephropathy, and neuropathy, supporting earlier findings that a 10% increase in TIR can reduce complication risks by up to 64%. Like the current article, Goshrani et al. emphasize the clinical superiority of TIR in vulnerable populations, including individuals with chronic kidney disease, pregnant women, and the elderly—groups where HbA1c is known to yield less reliable readings due to confounding factors like altered erythrocyte turnover, anemia, or physiological glycation shifts. Additionally, they address the lack of standardization in CGM systems and the variability in sensor calibration and wear-time, reinforcing concerns outlined here regarding methodological heterogeneity across devices. Importantly, both studies converge on the recommendation that TIR should not replace HbA1c outright but rather serve as a powerful adjunct that enhances daily management, enables individualized therapy, and captures glycemic fluctuations invisible to averaged biomarkers. In this context, Goshrani et al. lend further credence to the proposal that TIR represents a clinically actionable and patient-centric evolution in diabetes care.[59]

The foundational relationship between Time in Range (TIR) and Hemoglobin A1c (HbA1c) was systematically explored by Vigersky and McMahon.,[60] whose analysis remains one of the earliest and most cited works substantiating the clinical relevance of TIR as a CGM-derived metric. In their study, they demonstrated a strong inverse linear correlation between TIR and HbA1c, quantitatively estimating that each 10% increase in TIR corresponds to an approximate 0.8% reduction in HbA1c. This empirical relationship not only validates TIR as a meaningful surrogate for average glycemic exposure but also forms the mathematical basis for modern CGM interpretations such as the Glucose Management Indicator (GMI). Their findings are consistent with the evidence presented in this article and reinforce the proposition that TIR offers a granular, day-to-day reflection of glucose control, which complements the broader, retrospective average captured by HbA1c. By bridging CGM-based analytics with traditional laboratory markers, the work of Vigersky and McMahon laid essential groundwork for the widespread clinical adoption of TIR as a co-primary endpoint in diabetes care.[60]

Kalra et al.,[61] offer key clinical insights into the importance of individualizing Time in Range (TIR) targets, particularly in the context of insulin therapy and diverse patient populations. Their multinational consensus panel emphasized that while a general TIR goal of >70% remains appropriate for most adults with diabetes, this target must be adapted based on patient-specific factors such as age, comorbidities, risk of hypoglycemia, and life expectancy. These recommendations directly support the notion presented in this article that TIR is not a one-size-fits-all metric but rather a flexible, patient-centric tool that can be tailored to optimize outcomes. Moreover, Kalra et al. highlighted the complementary role of TIR alongside HbA1c in guiding therapeutic decisions, especially in insulin-treated patients, where day-to-day glycemic fluctuations carry significant clinical risk. Their findings underscore the practical value of integrating TIR into individualized care pathways, aligning with the broader argument advanced in this review—that TIR enhances therapeutic precision, captures dynamic glucose trends, and empowers clinicians to deliver more nuanced diabetes management.[61]

Pujante Alarcón et al.,[62] provide valuable real-world evidence supporting the correlation between continuous glucose monitoring (CGM) metrics—particularly those derived from flash glucose monitoring—and HbA1c in routine clinical practice. Conducted in Asturias, Spain, their study analyzed a diverse cohort of patients with diabetes and found that CGM-derived parameters such as TIR, Time Above Range (TAR), and Time Below Range (TBR) show statistically significant correlations with laboratory-measured HbA1c. However, the study also highlighted individual variations, especially among patients with different durations of diabetes, BMI, and insulin regimens, underscoring the limitations of relying solely on HbA1c to assess glycemic control. These findings align with the argument presented in this article—that while HbA1c remains a foundational biomarker, CGM metrics like TIR offer more dynamic and individualized insights into daily glycemic variability. The authors advocate for broader integration of TIR into diabetes care, echoing the call for multi-metric analysis to better capture real-life glycemic exposure and risk, particularly in complex or heterogeneous patient populations.[62]

Battelino et al.,[45] established landmark recommendations through the International Consensus on Time in Range, offering standardized clinical targets for interpreting continuous glucose monitoring (CGM) data across various patient populations. Their consensus defined TIR thresholds tailored to age, risk profile, and clinical context—for example, recommending >70% TIR for most adults with diabetes and more relaxed targets (>50%) for high-risk groups such as the elderly or those with comorbidities. They also emphasized limits on Time Below Range (TBR) and Time Above Range (TAR) to reduce hypoglycemia and hyperglycemia-associated risks. These guidelines have become foundational in CGM-based care and are frequently cited to support

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J.* 2025;13(2):46‒61.
DOI: 10.15406/emij.2025.13.00370

individualized and evidence-based glucose management. Their work aligns closely with the present article's emphasis on CGM-derived metrics—particularly TIR—not only as complementary to HbA1c but also as critical to optimizing patient safety and outcomes. The adoption of these consensus targets further legitimizes the clinical relevance of TIR and supports its integration into both research protocols and everyday diabetes care.[45]

Hallström et al.,[63] conducted a detailed analysis of CGM metrics in individuals with both type 1 and type 2 diabetes treated with multiple daily insulin injections (MDI), providing important insights into the practical utility of Time in Range (TIR) across insulin-intensive therapy settings. Their study found that while TIR values varied by diabetes type and demographic characteristics, they consistently demonstrated a strong inverse correlation with HbA1c. Importantly, they highlighted that patients with higher TIR not only had lower HbA1c levels but also experienced reduced glycemic variability and fewer episodes of hypoglycemia. These findings reinforce the position advanced in this article—that TIR is a clinically meaningful metric that complements HbA1c, especially in insulin-treated populations where day-to-day fluctuations and risk of hypo- or hyperglycemia are most pronounced. By characterizing CGM-derived outcomes in real-life MDI users, Hallström et al. support the growing consensus that TIR enables a more responsive and individualized approach to diabetes management than HbA1c alone.[63]

Moscardó et al.,[64] provided a methodological comparison of various glucose control metrics by applying discriminant ratio analysis to evaluate their effectiveness in distinguishing between individuals with differing levels of glycemic control. Their results demonstrated that Time in Range (TIR) outperformed other CGM-derived metrics—including mean glucose, standard deviation, and coefficient of variation—in its discriminative power relative to HbA1c. This analytical advantage supports the use of TIR not only as a clinical monitoring tool but also as a statistically robust outcome measure in diabetes research. The findings align with the current article's argument that TIR offers superior real-time granularity and predictive relevance compared to traditional markers. By showing that TIR captures meaningful clinical differences more effectively than other metrics, Moscardó et al. substantiate the growing consensus that TIR should be prioritized in both clinical trials and routine diabetes care as a key performance indicator of glycemic control.[64]

He et al.,[65] argued convincingly that glycated hemoglobin (HbA1c) alone is insufficient for comprehensive glycemic assessment, especially in individuals with type 1 diabetes. Their study introduces the Glycemia Risk Index (GRI) as a complementary CGM-derived metric that captures both hypo- and hyperglycemia risk more effectively than HbA1c. By analyzing real-world data, they demonstrated that patients with similar HbA1c levels can exhibit widely different glycemic patterns and risk profiles—differences that are more clearly illuminated through metrics such as TIR, TBR, and GRI. These findings strengthen the central argument of this article: that HbA1c, while foundational, fails to account for glycemic variability and acute glucose excursions that have substantial clinical implications. He et al. advocated for the routine incorporation of multi-metric CGM analysis, including TIR and GRI, to enable a more nuanced and individualized approach to diabetes management. Their work highlights the potential for CGM metrics to refine risk stratification and improve outcomes beyond what HbA1c alone can offer.[65]

Overall, the inclusion of these studies substantiates the manuscript's proposal that TIR is a clinically valuable and technically superior adjunct to HbA1c. The discussion should reflect how these external findings converge with the article's arguments, especially regarding microvascular risk, individualized targets, and the limitations of relying solely on HbA1c.

Key takeaways on CGM and Time in Range (TIR)

Continuous Glucose Monitoring (CGM) metrics have become increasingly standardized and more accessible to both patients and healthcare professionals, though some barriers to widespread adoption still exist. Among these metrics, Time in Range (TIR) is rapidly emerging as a valuable predictor of long-term diabetes complications. Beyond its clinical utility, TIR is an intuitive and patient-friendly metric that strongly correlates with patients' perceived success in diabetes management and their overall mood and well-being.

All CGM-derived metrics and reports serve as powerful tools for clinicians, enabling efficient assessment of glycemic status and facilitating personalized treatment adjustments on time. Furthermore, empowering patients through education on how to recognize and respond to glycemic patterns and trends can enhance their ability to reach and maintain their target TIR. This approach not only supports better clinical outcomes but also reinforces the patient's sense of control and achievement in managing their diabetes.

Barriers for CMG

A. Lack of standardization: different CGM devices (Dexcom, Libre, Medtronic) vary in calibration, sampling frequency, and accuracy, which will lead to complicated cross-study comparison

B. Sensor wear time: studies use different durations (e.g., 7 vs 14 days), affecting TIR estimates

C. Data completeness: minimum 70@ sensor wear is recommended, but adherence varies

D. In clinical practice: some sensors are affected by medications (acetaminophen, hydroxyurea) or physiological state (e.g., hypotension), limited access and training; moreover, TIR goals vary for most adults and pregnant women, therefore mandating nuanced interpretation.

Continuous Glucose Monitoring systems offer transformative benefits for diabetes management, but several barriers still limit their widespread adoption. Here's a structured overview of the most reported challenges identified through the patient questionnaire (Figure 15).[66–70]

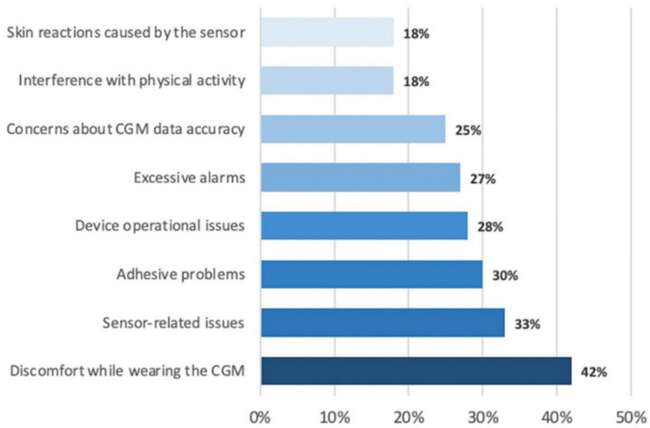

Figure 15 Reported barriers to Continuous Glucose Monitoring (CGM) use, courtesy of Journal of Diabetes Investigation.[71]

Conclusion: Can TIR replace A1C?

TIR provides insight into the current quality of glucose control over a short period, typically 10 to 14 days, using Continuous Glucose Monitoring (CGM) systems. It offers valuable data on the variability of glucose levels throughout the day, which is not captured by A1C. Due to its detailed and dynamic nature, TIR is increasingly regarded as a promising tool for improving diabetes management, particularly in daily clinical practice.

However, while TIR offers important advantages, it should not be seen as a direct replacement for HbA1c. Currently, no universal standards exist for glucose measurements across different CGM systems, and variability in device accuracy can result in discrepancies between readings. Additionally, despite its growing popularity, there is still a lack of robust, large-scale data confirming the correlation between CGM-derived metrics and long-term clinical outcomes. Thus, TIR should be regarded as a complementary tool rather than a substitute, offering additional, real-time information to guide therapy alongside the established role of HbA1c in assessing long-term glycaemic control.

Acknowledgments

1) I extend my heartfelt gratitude to Mr. Surinderpal Singh and Ajanta Pharma Group for the generous invitation to present at ACME, held in Rome, Italy, on May 16–17, 2025. His unwavering support and warm hospitality greatly enriched the experience and contributed to the success of this research.
2) Sincere gratitude to Mr. Ammar S. AlJadir, MSc, for his invaluable assistance in script finalization and overall arrangement. His meticulous attention to detail and unwavering support greatly enhanced the quality of this work.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Funding

None.

References

1. Vucic Lovrencic M, Topic E. Hemoglobin A1c: Standardization of the "gold standard." *Biochem Medica*. 2006;16(1):25–36.
2. World Health Organization (WHO). *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation.* 2011.
3. National Institute of Diabetes and Digestive and Kidney Diseases. NGSP: Clinical Use. *ngsp.org*. 2025.
4. Mayo Clinic. Glucose tolerance test. *mayoclinic.org*. 2024.
5. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the ADA and the EASD. *Diabetes Care*. 2022;45(11):2753–2786.
6. Diabetes Australia. Hypoglycaemia and hyperglycaemia. *Diabetes Australia*. 2025.
7. Centers for Disease Control and Prevention (CDC). Testing for diabetes and prediabetes: A1C. *Diabetes*. 2024.
8. American Diabetes Association. Understanding diabetes diagnosis. *diabetes.org*. 2023.
9. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care*. 2023;46(10):e151–e199.
10. Bugge SK, Fathima T. Comparison of HbA1c estimation by enzymatic and HPLC methods. *Indian J Med Biochem*. 2024;27(3):53–56.
11. Kanmaz-Ozer G, Genc S, Gurdol F, et al. The analytical performances of four different glycated methods. *Med Chem*. 2014;4(6):501–505.
12. Devkota BP. Hemoglobin A1c testing. *Medscape.com*. 2019.
13. Nathan D. Estimated average glucose (eAG) from HbA1c. *MDCalc*. 2024.
14. A1c conversion chart: A1c to mg/dL to mmol/L. *My Medical Score*. 2019.
15. IFCC Network for Standardization of HbA1c. *ifcchba1c.org*. 2023.
16. Consensus Committee. Consensus statement on the worldwide standardization of the hemoglobin A1c measurement. *Diabetes Care*. 2007;30(9):2399–2400.
17. Kunkel HG, Wallenius G. New hemoglobin in normal adult blood. *Science*. 1955;122(3163):288.
18. Camarena-Hidalgo MS, Meaney E, Ortiz-Vilchis P. Fundamentals of glycated hemoglobin: Value and benefits in clinical practice. *Cardiovasc Metab Sci*. 2023;34(3):119–126.
19. Ioannou A, Varotsis C. Modifications of hemoglobin and myoglobin by Maillard reaction products. *PLoS One*. 2017;12(11):e0188095.
20. Bolt HM, Hengstler JG. Trends in research on advanced glycation end products (AGEs). *Arch Toxicol*. 2024;98(11):3515–3517.
21. Ioannou A, Varotsis C. Probing hemoglobin glyco-products by fluorescence spectroscopy. *RSC Adv*. 2019;9(64):37614–37619.
22. American diabetes association. Understanding A1C. *diabetes.org*. 2023.
23. Creative Proteomics. Glycosylation vs glycation: Similarities and differences. *creative-proteomics.com*. 2022.
24. Rédaction Supersmart. Glycation: the silent process that accelerates ageing. *supersmart.com*. 2020.
25. Team TG. Glycation vs glycosylation: What's the difference? *glycanage.com*. 2025.
26. Lakna. What is the difference between glycation and glycosylation? *pediaa.com*. 2018.
27. Creative Biolabs. Glycosylation vs glycation: What is the difference? *creative-biolabs.com*. 2025.
28. He M, Zhou X, Wang X. Glycosylation: mechanisms, biological functions and clinical implications. *Signal Transduct Target Ther*. 2024;9(1):194.
29. National Library of Medicine. Abnormal glycosylation (Concept Id: C4022946). *MedGen*. 2020.
30. Ram Y, Kaufman T, Pinhas-Hamiel O, et al. Variation in the relationship between fasting glucose and HbA1c: implications for the diagnosis of diabetes in different age and ethnic groups. *BMJ Open Diabetes Res Care*. 2024;12(2):e003470.
31. Kasujja FX, Rwibuka C, Ssentongo P, et al. Glycated haemoglobin versus fasting plasma glucose for type 2 diabetes point of care screening: a decision model cost-effectiveness analysis. *BMC Health Serv Res*. 2025;25(1):664.
32. DiMagno T. Hemoglobin A1c: Summary of existing test methods and introduction of a novel assay design. *APFCB*. 2022;1(2):88–101.
33. Mahabeer S. HbA1c measurement and assay interferences. *LANCET*. 2018.

34. Almeshari H, Othman H, Mahzari M, et al. Correlation between HbA1c levels and microvascular complications in type 2 diabetes. *Int J Sci Technol*. 2024;15(1).

35. Setareh J, Ghasemi H, Ebrahimi M, et al. Can the level of HbA1c predict diabetic retinopathy among type II diabetic patients? *BMC Ophthalmol*. 2022;22(1):415.

36. Medcrine. HbA1c Test: Physiology and interpretation of results. *medcrine.com*. 2025.

37. Shetty A. Hemoglobin A1C. *pathologyoutlines.com*. 2022.

38. Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Arch Public Health*. 2015;73(1):43.

39. Perry RC, Shankar RR, Fineberg N, et al. HbA1c measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). *Diabetes Care*. 2001;24(3):465–471.

40. Lee JE. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol. *Ann Pediatr Endocrinol Metab*. 2015;20(2):74–78.

41. Cleveland Clinic. Time in range for diabetes: What it is & target. *clevelandclinic.org*. 2024.

42. Novo MedClinic. Time in range targets & guidelines for diabetes. *novo medlink*. 2024.

43. American Diabetes Association. CGM & time in range. *diabetes.org*.

44. Wright EE, Hirsch IB, Gilliam LK, et al. Time in range: clinical decision--making. *Clin Diabetes*. 2020;38(5):439–448.

45. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593–1603.

46. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593–1603.

47. Raj R, Swamy S, Soni A, et al. Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review. *BMJ Open Diabetes Res Care*. 2022;10(1):e002573.

48. Time in Range. Time in range in 2024 ADA standards of care. *Time in Range Coalition*. 2024.

49. ElSayed NA, Aleppo G, Aroda VR, et al. Glycemic targets: Standards of care in diabetes—2023. *Diabetes Care*. 2022;46(Suppl 1):S97–S110.

50. Skyler JS. Effects of glycemic control on diabetes complications. *Clin Diabetes*. 2004;22(4):162–166.

51. Dexcom. Time in range for diabetes management with CGM. *Dexcom.com*. 2019.

52. Olansky L, Kennedy L. Finger-stick glucose monitoring: Accuracy and specificity. *Diabetes Care*. 2010;33(4):948–949.

53. Aleppo G. Clinical application of time in range and other metrics. *Diabetes Spectr*. 2021;34(2):109–118.

54. Diabetes UK. Closed-loop systems (artificial pancreas). *diabetes.org.uk*. 2022.

55. Alyson PK. How does a CGM sensor work? *wellwisp.com*. 2025.

56. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care*. 2018;42(3):400–405.

57. Mayeda L, Katz R, Bernatsky S, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. *BMJ Open Diabetes Res Care*. 2020;8(1):e000991.

58. Lu J, Ma X, Shen Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther*. 2020;22(2):72–78.

59. Goshrani A, Patel H, Vyas A, et al. Time in range: A new gold standard in type 2 diabetes research? *Diabetes Obes Metab*. 2025;27(5):2342–2362.

60. Vigersky R, McMahon C. SAT-126 the relationship of continuous glucose monitoring (CGM)-derived time-in-range (TIR) to hemoglobin A1c (HbA1c). *J Endocr Soc*. 2019;3(Suppl 1):SAT–126.

61. Kalra S, Shehla S, Gagan P, et al. Individualizing time-in-range goals in management of diabetes mellitus and role of insulin: clinical insights from a multinational panel. *Diabetes Ther*. 2021;12(2):465–485.

62. Pujante Alarcón P, García Mayo EJ, González del Valle E, et al. Correlation between glucose measurement parameters of continuous flash monitoring and HbA1c. Real life experience in Asturias. *Endocrinol Diabetes Nutr*. 2022;69(7):493–499.

63. Hallström S, Witsch M, Löfgren UB, et al. Characteristics of continuous glucose monitoring metrics in persons with type 1 and type 2 diabetes treated with multiple daily insulin injections. *Diabetes Technol Ther*. 2021;23(6):425–433.

64. Moscardó V, Rojas R, Ferré J, et al. Assessment of glucose control metrics by discriminant ratio. *Diabetes Technol Ther*. 2020;22(10):719–726.

65. He BB, Zhang Y, Wang P, et al. Glycated hemoglobin is not enough: Role of glycemia risk index. *World J Diabetes*. 2025;16(6):104024.

66. Cleveland Clinic. Continuous glucose monitor (CGM). *clevelandclinic.org*. 2024.

67. Edelman SV, Argento NB, Pettus J, et al. Clinical implications of real-time and intermittently scanned CGM. *Diabetes Care*. 2018;41(11):2265–2274.

68. Tandem Cares. What is a hybrid closed-loop insulin pump system? *Tandem Diabetes Care*. 2022.

69. Bender C, He B, Wang Z. History, evolution, and future of CGM. *Diabetology*. 2025;6(3):17.

70. Lu J, Wang C, Shen Y, et al. Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: a prospective cohort study. 2021;44(2):549–555.

71. Chen H, Lai Y, Jiang Y. Overcoming barriers in continuous glucose monitoring: Challenges and future directions in diabetes management. *J Diabetes Investig*. 2025;16(5):769–774.

Citation: AlJadir SJS. Time-in-Range Vs. HbA1c: Is it time to retire the gold standard? *Endocrinol Metab Int J*. 2025;13(2):46–61.
DOI: 10.15406/emij.2025.13.00370