

REVIEW ARTICLE

Continuous Blood Glucose Monitoring: Potential Applications from Diabetes Management

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ABSTRACT

Continuous glucose monitoring (CGM) is a transformative technology in diabetes management. By providing real-time interstitial glucose readings, CGM offers insights into glycemic patterns that were previously inaccessible with traditional self-monitoring of blood glucose. This review delves into the fundamentals of CGM, including sensor technology, placement considerations, and factors affecting measurement accuracy. Various CGM-derived metrics, such as Time in Range (TIR), Ambulatory Glucose Profile (AGP), Continuous Overall Net Glycemic Action (CONGA), and Mean of Daily Differences (MODD), are examined, highlighting their distinct roles in assessing glycemic control. This review discusses the current clinical applications of CGM and its potential benefits for personalized therapy and patient self-management. Furthermore, this review explores ongoing research to refine CGM technology, develop novel metrics, and expand its applications beyond established diabetes care into areas such as prediabetes and athletic performance. Ultimately, CGM is poised to play an increasingly central role in optimizing glucose control, reducing diabetes-related complications, and improving the quality of life in individuals with diabetes.

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INTRODUCTION

Continuous Glucose Monitoring (CGM) technology has significantly impacted diabetes treatment by providing real-time information about glucose levels and enabling individuals to make informed decisions about their treatment. Studies have shown that CGM systems offer valuable insight into glucose histories and trends, allowing users to optimize diabetes self-management (1-4). The benefits of CGM in diabetic treatment are well established, and there is evidence that it can improve blood sugar control by reducing Hemoglobin A1c (HbA1c) levels (2). Furthermore, CGM has been associated with improved health outcomes for patients with diabetes, highlighting its potential to improve overall glycemic control, reduced hypoglycemic episodes, fewer hospital visits, decreased absenteeism, and ultimately reduced healthcare costs (3). Research has confirmed the effectiveness of CGM in various populations, including adults, adolescents, and young children with Type 1 Diabetes (T1D). While most studies focused primarily on adults using insulin pumps,

a recent study has highlighted the positive effects of CGM usage over 24 weeks on individuals using insulin pumps or injections, adolescents, and young adults by improving the HbA1c reading (4). A study suggested that CGM is safe to be used on young children (4 to <10 years old) with T1D, but did not improve blood sugar control compared to usual care. However, it is important to note that CGM adherence was a challenge in this population, which could have impacted the results (5). The use of CGM devices has not only improved diabetes outcomes but has also positively impacted the quality of life in adults with diabetes. The technology has been proven to reduce diabetes management burden, increase satisfaction with glucose monitoring, and reduce perceived barriers to using technology in treatment, ultimately increasing users' overall well-being (6). Additionally, CGM has helped adolescents engage with diabetes treatment, fostered a sense of belonging and normalcy, and facilitated better treatment outcomes and quality of life (7). Owing to its increased measurement frequency and reduced invasiveness, CGM technology has recently seen expanded applications beyond diabetes management. This shift has led to investigations into CGM's efficacy in diverse populations.

In intensive care settings, CGM has been used to understand the dynamic nature of glucose regulation

and to address how different locations of sensor placement can influence the complexity of CGM data in this population to manage stress-induced hyperglycemia among patients, providing real-time glucose monitoring to aid in precise glucose management (8). Similarly, in neonatal care, CGM has been explored to prevent hypoglycemia in newborns. However, its effectiveness and accuracy in these settings vary and must be addressed regarding errors in blood glucose calibration measures (9). The potential benefits of CGM in athletes have also been considered, although research in this area is still developing. Optimizing athletes' blood glucose levels could hold promise for enhancing race performance, expediting recovery, and improving training outcomes, yet further study is required for optimization (10-12). Studies have delved into glucose dynamics in endurance and ultra-endurance athletes, aiming to elucidate glucose responses during competitions (13-15) and everyday activities (10, 12). On top of that, researchers have established reference ranges for sensor glucose in healthy individuals across different age groups, providing valuable insights into normal glucose regulation (16). Furthermore, CGM's potential to enhance nutritional and physical activity behaviors in healthy adults has been acknowledged, as it can detect abnormal glucose levels and potentially improve performance and recovery from physical activities (17).

This review paper examines the potential of applying CGM technology beyond its established role in diabetes management, specifically focusing on non-diabetic populations. By leveraging the extensive research and advancements in diabetes care, this review aims to evaluate the feasibility of adapting CGM for broader use. We will begin by exploring the principles of CGM operation, highlighting its advantages and limitations. The review will then critically examine how critical aspects of CGM utilization, including sensor technology, placement considerations, accuracy metrics, and methods for analyzing glycemic variability, might be applied and optimized for non-diabetic populations. Through this analysis, we seek to address unique challenges and considerations that possibly arise in using CGM outside the context of diabetes, paving the way for potential benefits in other areas of health and wellness.

CGM DEFINITION AND FUNCTION

Continuous Glucose Monitoring (CGM) devices detect glucose levels by measuring changes in interstitial glucose values, providing insights into glucose levels (18). The systems consist of a sensor placed in subcutaneous tissue to measure glucose levels in interstitial fluid, transmitting data wirelessly to a receiver or a smartphone for analysis and display. These systems provide detailed information on glucose levels, including trends, alerts for both hypoglycemia and hyperglycemia, and glycemic variability. It alerts for impending glucose

fluctuations and continuous coverage (19).

Monitoring the glucose level can be done either in real-time or retrospectively. Flash Glucose Monitoring (FGM) and Real-Time Continuous Glucose Monitoring (RT-CGM) are two types of glucose monitoring systems with distinct features. FGM, like the FreeStyle Libre (Abbott Laboratories, Malaysia), allows users to retrospectively review glucose data from the past 8 hours, providing estimated blood glucose values and trend lines without real-time alerts (20, 21). On the other hand, RT-CGM systems offer continuous real-time glucose data, trend analysis, and alerts for hypoglycemia and hyperglycemia, facilitating prompt actions in response to glucose fluctuations (22, 23).

A study has shown that RT-CGM has a greater beneficial impact on hypoglycemia compared to FGM in adults with T1D at high risk of hypoglycemia, and continuing use can maintain its benefit (23). RT-CGM systems provide immediate information about current and projected glucose levels, enabling users to respond promptly to prevent impending hypoglycemia or hyperglycemia (3). This real-time data can be useful during exercise when glucose levels fluctuate rapidly. However, it is important to note that while RT-CGM and FGM can provide valuable information during exercise, their accuracy is limited. In particular, RT-CGM readings may lag behind actual blood glucose changes during exercise, potentially leading to inaccurate readings. This lag can make it challenging for individuals, especially those with T1D, to rely solely on RT-CGM to guide carbohydrate intake and avoid hypoglycemia (low blood sugar) during exercise (24). To address those limitations, innovative technologies such as multi-sensor integration, calibration algorithms, and machine learning can be considered to enhance accuracy and reliability. These advancements, coupled with nutritional or medical advice, can empower both individuals with diabetes and healthy athletes to utilize CGM effectively and safely for informed glucose management (25).

NEW TECHNOLOGY IN CGM

Nanotechnology has significantly impacted the field of glucose monitoring, particularly in the development of more compact and comfortable CGM systems. The sensitivity, accuracy, and speed of glucose detection have all been improved by nanotechnology through the creation of nanoscale sensors, an increase in sensor surface area, and an improvement in electrode catalytic properties (26). Advancements in CGM technology include its compact size, discreet devices with enhanced accuracy, and remote monitoring capabilities, which hold great promise for optimizing glycemic outcomes in individuals with diabetes, as evidenced by the improved glycemic control and reduced hospitalizations observed in pediatric patients using CGM technology (27). Continued innovation in this field has the potential to

revolutionize diabetes management further and improve the quality of life for individuals living with this condition (27, 28).

Recent updates in CGM technology have introduced factory-calibrated systems, which have significantly improved accuracy compared to previous generations of CGM devices. These factory-calibrated CGM systems leverage advances in sensor chemistry and CGM algorithms to enhance accuracy, making them more reliable for glucose monitoring. The calibration process is simplified with factory-calibrated systems, eliminating the need for manual calibration by the user and reducing potential errors associated with calibration (29).

Moreover, the development of new low-cost, factory-calibrated CGM sensors and the approval of marketed CGM sensors for making treatment decisions can potentially revolutionize the use of CGM technology. These advancements in CGM technology aim to enhance diabetes management by providing more accessible and accurate glucose monitoring solutions through an established data ecosystem (30). Recent improvements in CGM accuracy pave the way for potential nonadjunctive use of CGM for diabetes treatment decisions, indicating a shift towards relying on CGM values alone for managing glucose levels (31). In managing diabetes, CGM can be used complementarily or integrated with other technologies or techniques. It has been experimentally demonstrated by Būzieux et al. (32) that integrating CGM with smartphone apps can capture visual dietary history and synced with measurement from CGM can provide valuable information which the data is simple to capture and reduce the burden on participants. Complimenting the visual with precise annotation can provide a more precise estimation, thus producing a high-quality measurement of relevant endpoints and enabling granular monitoring of subject compliance with low clinical overhead (32).

A study that evaluates the feasibility of administrating CGM through telehealth showed improvements in glycaemic outcome with HbA1c reading of 34 subjects from 8.3% to 7.2%, mean time in range (70-180 mg/dL, 3.9-10.0 mmol/L) improved from 48% to 59% and mean glucose concentration decreasing from 196 ± 46 mg/dL (10.9 ± 2.6 mmol/L) at baseline to 170 ± 36 mg/dL (9.4 ± 2.0 mmol/L). The participants showed high satisfaction, trust, hypoglycemia confidence, diabetes technology attitudes, and decreases in diabetes management distress, emotional burden, and behavioral burden (6). The results of another study by Zahedani et al. (33) provided new and vital insights into the use of CGM-related technology to identify at-risk individuals with postprandial glucose dysregulation and its potential to improve glycaemic control in these individuals and individuals with Type 2 Diabetes (T2D). In particular, the results showed that a multimodal approach that includes CGM, food, and activity logging with data synthesis and

continuous feedback through a smartphone application showing an overlay of glucose curves on food choice and physical activity, as well as glycaemic index/glycaemic load and macronutrient tracking, can achieve improvement in self-described healthy, prediabetic and type T2D groups. It can also improve consumer knowledge about healthy food choices by allowing the consumer to evaluate the effects on glucose response rather than relying on the food label and advertising. Besides enhancing glycemic control of T2D patients, this multimodal approach intervention is potentially crucial for the healthy population with the earliest postprandial glucose dysregulation and those with prediabetes, as it occurs at an early stage before the diagnosis of T2D and associated T2D starting to change their diet can cause symptoms (e.g., insulin resistance) and are therefore likely to delay the onset of T2D (33).

SENSOR PLACEMENT

Sensor placement ensures accurate and reproducible glucose concentration output while providing a comfortable, pain-free experience during wear. The performance of the CGM system was evaluated by comparing the blood glucose results between sensor placement in the back of the upper arm and the abdominal wall in patients with diabetes. According to the study, the blood glucose reading obtained from the upper arm CGM placement can be utilized as a somewhat appropriate supplementary tool in treating and managing diabetes (34).

A study on 23 healthy adults by Kawakatsu et al. (35) evaluated the mean difference in glucose levels between the right and left arms and showed significant differences in mean glucose levels between both arms, with the right arm's mean glucose level being higher by 3.7mg/dL (0.2 mmol/L). The results showed similar patterns during intermittent fasting and free-living states. This difference could lead to miscategorization of glycaemic reading and subsequently influence the effectiveness of glycaemic management in both healthy and diabetic patients (35).

Coates et al. (36) recently discovered in a group of cyclists that while the accuracy of readings in both triceps brachii (traditional) and vastus medialis (active muscle) were the same, especially during active and passive thigh muscle contraction (cycling and muscle stimulation), wearing sensors on active muscle may provide greater insight into glucose delivery and uptake of the targeted muscle.

MEASURES OF ACCURACY

The Mean Absolute Relative Difference (MARD) has been used to evaluate the accuracy of CGM as a system rather than the sensor alone, meaning that the performance of CGM depends on the sensor and

algorithm. It quantifies the average difference between CGM values and reference glucose values, providing a measure of the overall accuracy of the CGM system. The MARD is calculated as the mean of the absolute relative differences between the CGM values and the corresponding reference glucose values (usually using capillary blood sugar values) (36). It is widely used to describe the accuracy of CGM systems and is routinely calculated and reported as a key performance metric by manufacturers. It is an important parameter for evaluating the reliability and precision of CGM systems, particularly in assessing their accuracy across different glycemic ranges. Also, as defined by Freckmann et al. (37), MARD quantifies the overall accuracy of CGM systems by presenting the average relative difference between CGM readings and reference glucose readings. The standard deviation of MARDs obtained over multiple sensor sessions further quantifies the variability or inconsistency of CGM accuracy over time and reflects the precision of the system (37).

The quality of the CGM sensor itself is not the sole factor affecting MARD values; variation in MARD throughout the day is potentially influenced by physiological conditions, such as the rate of glucose changes during the assessment, which also significantly impacts MARD accuracy (38). Studies comparing intravascular and subcutaneous CGM systems have shown differences in performance, with factors like lag time between blood and interstitial compartments influencing MARD values (39, 40). This delay can potentially lead to reduced measurement accuracy, particularly during periods of rapidly changing glucose concentrations, as demonstrated by studies examining the performance of subcutaneous CGM systems during induced glucose swings (41). Faster rates of glucose concentration change may exacerbate this apparent decrease in accuracy, potentially highlighting a greater advantage for intravascular CGM systems in these scenarios.

Pleus et al. (38) demonstrated that the accuracy of CGM systems, as measured by MARD, exhibits significant diurnal variation. Values of MARD were lowest during fasting states and increased substantially following meals, highlighting performance limitations when blood glucose levels change rapidly (38). This variability in accuracy extends beyond mealtimes and is particularly pronounced during exercise. The accuracy of CGM systems during exercise remains a challenge in blood glucose management. Physiological changes associated with physical activity, such as increased blood flow and glucose fluctuation (42), can disrupt sensor performance and glucose diffusion, leading to discrepancies between CGM readings and actual blood glucose levels, especially during aerobic exercise (24). Moreover, challenges in maintaining frequent calibration during exercise can further compromise data reliability (18). Individual variability in physiological responses to exercise adds another layer of complexity, making it difficult to

achieve consistent CGM accuracy across different individuals and exercise intensities (43, 44). Variability in CGM data observed during high-intensity intervals or endurance exercises leads to varying MARD values (36). Therefore, the accuracy of CGM devices, as represented by MARD, cannot be distilled into a direct comparative analysis, given the intricate interplay of factors that can influence their performance. This variability in MARD can be attributed to factors illustrated in Table I.

Table I: Factors affecting the variability of MARD

Author	Factor	Findings
Rodbard 2016 (19)	Sensor calibration, Algorithm design	Calibration accuracy and algorithms influence overall CGM performance.
Zaharieva et al., 2019 (24), Fabra et al., 2021 (63)	Physical activity, intermittent and aerobic	Exercise can induce physiological changes, negatively impacting CGM readings.
Zaharieva et al., 2019 (24), Schmelzeisen et al., 2015 (64)	Interstitial fluid vs. Blood glucose	The lag between compartments causes temporary inaccuracies, especially during rapid changes.
Pleus et al., 2022 (38)	Time of day, Blood glucose dynamics	MARD fluctuates throughout the day and is highest post-meal.
Pleus et al., 2015 (41)	Rate of change, Hypoglycemia	MARD is higher during fast glucose changes, and hypoglycemia affects accuracy.
Kropff et al., 2017 (65)	Sensor wear time	Sensor performance may degrade slightly over its lifespan.
Aberer et al., 2017 (66)	Hypoglycemia	CGM performance can be impacted in hypoglycemia ranges.

READING THE BLOOD GLUCOSE DATA

Standard Deviation (SD) and Coefficient of Variation (CV)

Standard Deviation (SD) and Coefficient of Variation (CV) are fundamental statistical tools for analyzing glycemic variability derived from CGM data where CV as a relative to mean can complement SD in describing glucose excursion. While extensively utilized, interpreting these measures in the context of optimal glycemic control while addressing the bias toward hyperglycemia can help evaluate the variability's outcome (45). Using CGM data to establish universal thresholds for 'normal' or 'high' SD and CV is complex. Optimal glycemic variability ranges likely differ based on individual patient factors, including diabetes type, treatment goals, risk of hypoglycemia, and other clinical characteristics. Although SD and CV can offer valuable insights, they should not be interpreted in isolation. They may fail to fully capture the impact of rapid glucose fluctuations or the pattern of variability. For a holistic understanding of glycemic control, these metrics need to be analyzed alongside clinical context and complementary measures, especially when dealing with the quality of glycemic control (46, 47).

Mean Amplitude of Glycemic Excursions (MAGE)

Mean Amplitude of Glycemic Excursions (MAGE) is a metric used to quantify glycemic variability in individuals with diabetes. It is calculated as the mean of absolute values of glucose differences between consecutive peaks and nadirs that are greater than one SD (48). It focuses on major variations in glycemic control, excluding minor fluctuations, providing valuable insights into glucose variability between days (49).

Research has shown the significance of MAGE in assessing glycemic variability and its impact on health outcomes. For example, MAGE has been significantly linked to cardiovascular outcomes in type 2 diabetic patients by detecting sympathovagal imbalance, indicating its possible role in predicting complications (50). It has also been used to evaluate the severity of hypoglycemia and glycemic lability in individuals undergoing islet transplantation, demonstrating its relevance in clinical settings (51).

While MAGE is commonly studied in diabetic populations, normal reference ranges for glycemic variability using continuous glucose monitoring in non-diabetic individuals have been established (52), providing valuable insights into typical glycemic fluctuations in healthy populations. Choudhary et al. (53) further emphasize the correlation between MAGE and oxidative stress markers in impaired glucose tolerance and impaired fasting glucose in children, highlighting the significance of glycemic variability even in the absence of diabetes. These references contribute to understanding MAGE in prediabetic populations, shedding light on the implications of glycemic variability in overall health.

Time in Range (TIR)

Time in Range (TIR), the percentage of time an individual's glucose levels remain within a specified target range (often 70-180 mg/dL, 3.9-10.0 mmol/L), has emerged as a vital metric derived from CGM data. In the context of diabetes management, TIR provides a nuanced and dynamic evaluation of glycemic control, complementing traditional measures such as HbA1c. Unlike HbA1c, which reflects an average glucose level, TIR elucidates fluctuations, hypoglycemic events, and overall glucose variability (54). Substantial research indicates a robust association between increased TIR and a diminished risk of both microvascular (e.g., retinopathy) and macrovascular complications (e.g., cardiovascular disease) in individuals with T1D and T2D (55, 56). Clinically, TIR facilitates the individualization of treatment strategies, guides new medication titration, and contributes to developing closed-loop insulin delivery systems in individuals with T1D (57).

The TIR's potential applications extend beyond established diabetes care. Studies in non-diabetic populations suggest that increased time spent above

target glucose ranges, even without a formal diagnosis, may signal an elevated risk for future T2D development (58). Additionally, TIR may hold value for specific populations, such as pregnant women diagnosed with gestational diabetes or athletes seeking to optimize performance and recovery strategies.

The Ambulatory Glucose Profile (AGP)

The Ambulatory Glucose Profile (AGP) is a standardized report that provides a visual and comprehensive summary of a person's glucose patterns over time. It represents a significant advancement in glucose monitoring for individuals with diabetes and potentially broader populations. Derived from CGM data, the AGP consolidates glucose readings over a specified period (typically 14 days) into a standardized visual report. This report offers a multi-dimensional perspective on glycemic patterns, including time spent within target glucose ranges, the extent of glucose fluctuations (upward and downward), and overall glucose variability. In contrast to the average value of HbA1c, the AGP's comprehensive view provides clinicians with insights for optimizing treatment strategies (57).

Continuous Overall Net Glycemic Action (CONGA)

Continuous Overall Net Glycemic Action (CONGA) is a metric derived from CGM data that quantifies the overall net changes in glucose levels over a specific period, considering both the magnitude and direction of fluctuations. It is calculated by summing the absolute differences between consecutive CGM readings. It provides a comprehensive view of glycemic variability by considering the cumulative effect of glucose excursions, offering a more nuanced perspective than simple metrics like SD that focus solely on the dispersion of values (59). The utilization of CONGA to differentiate individuals with T1D and healthy controls successfully showed that the diabetes group consistently exhibited higher CONGA values across all time intervals and generally increased as time interval increased compared to the control group. The study also revealed that substantial individual variability in CONGA value within the diabetes group suggests that CONGA can capture diverse patterns of glycemic instability (59).

The Mean of Daily Differences (MODD)

Glycemic variability is a crucial aspect of diabetes management, and the Mean of Daily Differences (MODD) is a metric used to assess day-to-day glycemic variability. It is calculated based on the absolute difference between paired CGM values obtained during two successive days (60, 61) and reflects between-day variability, making it a valuable tool for understanding fluctuations in glucose levels over time.

In women with a history of gestational diabetes mellitus (GDM), MODD may indicate a metabolic abnormality. For women with prior GDM and normal glucose tolerance (NGT), MODD was higher compared to

NGT women without prior GDM. In women who have previously had GDM, elevated glycemic variability, as determined by MODD, may be associated with early indicators of vascular dysfunction (62). Mean of Daily Differences has also been used as a primary marker in determining the factor influencing inter-day glycemic variability in diabetic outpatients receiving insulin therapy. Besides being associated with HbA1c and glycoalbumin levels, MODD can be used to assess the

impact of lifestyle and glycemic control on a day-to-day basis (60). The use of CGM, in conjunction with insulin pumps and closed-loop systems, is expected to enhance the clinical utility of CGM (19), with MODD aiding in understanding glucose fluctuations. Table II presents a simplified summary of glucose variability metrics, focusing on the most commonly used and clinically relevant indicators.

Table II: Metrics of glucose variability

Method	Description	Advantages	Considerations
Standard Deviation (SD)	Measures the spread of glucose values around the mean.	Straightforward calculation, easy to understand.	It can be affected by extreme values and does not consider the sequence of values.
Coefficient of Variation (CV)	SD standardized to the mean (expressed as a percentage).	Allows comparison of variability across different glucose ranges.	It is less intuitive for some users to interpret.
Time in Range (TIR)	Percentage of time spent within a target glucose range (e.g., 70-180 mg/dL).	It focuses on clinically relevant outcomes and is easy to understand.	Can mask both hypo and hyperglycemia if average glucose is in range.
Ambulatory Glucose Profile (AGP)	Graphical representation of CGM data across 24 hours, with median, interquartile ranges, etc.	Visualizes patterns suitable for identifying periods of variability.	It can be more complex for some users to interpret.
Mean Amplitude of Glycemic Excursions (MAGE)	Measures the average size of glucose swings.	Captures the magnitude of upward and downward fluctuations.	May overestimate variability if there are frequent small fluctuations.
Continuous Overall Net Glycemic Action (CONGA)	Assesses glucose variability based on rate of change over specific time intervals.	Captures speed and direction of fluctuations with more context than MAGE.	More complex calculation.
Mean of Daily Differences (MODD)	Calculates the average absolute difference between glucose values on consecutive days at the same time.	Captures day-to-day changes in glycemic patterns	Eating patterns, and time of day, can influence it

CONCLUSION

The application of CGM has transformed diabetes management, providing unprecedented real-time insights into glycemic dynamics that extend far beyond traditional blood glucose monitoring capabilities. A thorough understanding of CGM technology, sensor placement, accuracy considerations, and the rich landscape of CGM-derived metrics is essential for maximizing its clinical and patient-centered benefits. Metrics like TIR, AGP, CONGA, and MODD offer complementary perspectives on glycemic control. These tools empower clinicians and patients, facilitating personalized treatment strategies and fostering patient engagement. As CGM technology continues to evolve, advancements in accuracy, wearability, and cost-effectiveness will broaden its accessibility. Future research holds immense promise for the field of CGM. Investigations into further refinement of existing metrics and developing novel parameters will likely enhance our ability to target specific aspects of glycemic control. Exploring the prognostic value of CGM metrics in diverse populations remains an active study area. Besides, the integration of CGM with closed-loop insulin delivery systems and decision-support algorithms has the potential to revolutionize diabetes treatment, moving closer to automated glucose management. Beyond diabetes care, CGM applications expand into athletic performance optimization, prediabetes detection, and

broader metabolic health monitoring. The wealth of data generated by CGM necessitates advancements in data analytics and visualization tools to harness its power fully. Ultimately, CGM stands to significantly reduce diabetes-related complications while improving the quality and longevity of life for individuals with and without diabetes.

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