Effects of Body Composition and Serum Biochemical Parameters on the Accuracy of the FreeStyle Libre Flash Glucose Monitoring System: Postprint

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Abstract

Background: The clinical application of Flash Glucose Monitoring (FGM) systems is becoming increasingly widespread. During wear, FGM does not require fingerstick calibration and can continuously monitor for 14 days, providing a basis for clinical treatment. Therefore, its accuracy is particularly important.

Objective: To investigate the influence of body composition and serum biochemical indices on FGM sensor accuracy.

Methods: Patients with type 2 diabetes mellitus (T2DM) hospitalized in the Department of Endocrinology at the Second Affiliated Hospital of Zhengzhou University in 2022 were selected as study subjects. General patient data were collected through the electronic medical record system. FGM was used to detect patient glucose data and compare it with venous blood glucose, and patient body composition analysis data were collected. Fasting venous blood samples were collected from patients to analyze hematological parameters. Clarke Error Grid Analysis was used to evaluate FGM clinical accuracy. Patients were divided into an accurate group (MARD<10%, n=23) and an inaccurate group (MARD>20%, n=34) based on the Mean Absolute Relative Difference (MARD) of paired glucose values. Binary logistic regression analysis was used to analyze factors influencing FGM accuracy.

Results: A total of 694 pairs of glucose data from 154 patients were collected. Using venous blood glucose as the reference value, Clarke Error Grid Analysis was performed on FGM scanned glucose values. The results showed that 82.9% fell in Zone A, 16.9% fell in Zone B, 99.8% fell in Zones A+B, and 0.2% fell in Zone D, with a mean MARD of 12.7%. Patients in the inaccurate group had higher MARD and muscle mass, and lower uric acid, body fat mass, and

fat percentage than the accurate group (P<0.05). Male patients in the inaccurate group had lower uric acid, body fat mass, and fat percentage, and higher MARD values and muscle mass than the accurate group (P<0.05). Female patients in the inaccurate group had higher MARD values than the accurate group (P<0.05). Binary logistic regression analysis results showed that muscle mass and serum uric acid concentration were influencing factors of FGM accuracy (P<0.05).

Conclusion: The overall accuracy of FGM meets international standards. FGM sensor accuracy is related to uric acid levels and human muscle mass, but is not affected by electrolyte ions or other biochemical indices in the blood, and is also not interfered with by factors such as body water, body fat content, inorganic salt content, and fat thickness at the sensor wear site.

Full Text

Effect of Human Body Composition and Serum Biochemical Indicators on the Accuracy of Flash Glucose Monitoring System

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Abstract

Background: The clinical application of flash glucose monitoring system (FGM) is becoming increasingly widespread. FGM can be continuously monitored for 14 days and does not require fingertip blood correction during wear, providing a basis for clinical treatment. Therefore, the accuracy of FGM is particularly important.

Objective: To investigate the effect of human body composition and serum biochemical indicators on the accuracy of FGM sensors.

Methods: Patients with type 2 diabetes mellitus (T2DM) hospitalized in the Department of Endocrinology of the Second Affiliated Hospital of Zhengzhou University in 2022 were selected as study subjects. General data were collected through the electronic medical record system. Blood glucose was detected using FGM and compared with intravenous blood glucose, and patients' body composition analysis data were collected. Fasting venous blood was collected to analyze hematological parameters. The clinical accuracy of FGM was evaluated

using Clarke error grid analysis. Patients were divided into an accurate group (MARD<10%, n=23) and an inaccurate group (MARD>20%, n=34) based on the mean absolute relative difference (MARD) of paired blood glucose values. Binary logistic regression was used to analyze the influencing factors of FGM accuracy.

Results: A total of 694 pairs of blood glucose data from 154 patients were collected. Using venous blood glucose as the reference value, Clarke error grid analysis of FGM scan values showed that 82.9% fell in Zone A, 16.9% in Zone B, 99.8% in Zone A+B, and 0.2% in Zone D, with an average MARD of 12.7%. The inaccurate group had higher MARD and muscle mass, and lower uric acid, body fat mass, and fat percentage compared with the accurate group (P<0.05). In male patients, the inaccurate group had lower uric acid, body fat mass, and fat percentage, and higher MARD and muscle mass compared with the accurate group (P<0.05). In female patients, the inaccurate group had higher MARD compared with the accurate group (P<0.05). Binary logistic regression analysis showed that muscle mass and blood uric acid concentration were influencing factors of FGM accuracy (P<0.05).

Conclusion: The overall accuracy of FGM meets international standards. The accuracy of FGM sensors is related to uric acid level and human muscle mass, but is not affected by electrolyte ions and other biochemical indicators in blood, nor is it interfered with by factors such as human body water, fat content, inorganic salt content, and fat thickness at the sensor wearing site.

Keywords: Diabetes mellitus, type 2; Blood chemical analysis; Blood glucose self-monitoring; Flash glucose monitoring system; Root cause analysis

Introduction

With the development of blood glucose monitoring technology, the work patterns of medical staff are constantly changing. In 2016, the flash glucose monitoring system (FGM) was approved for market release by the China Food and Drug Administration. FGM can provide continuous glucose dynamic profiles for up to two weeks without requiring calibration with fingertip blood glucose. Since then, clinicians have gradually shifted from focusing on point-in-time glucose values to monitoring whether blood glucose is stable throughout the day. Related studies have shown that long-term glucose variability is an important cause of diabetic vascular complications in patients, and ensuring stable blood glucose during treatment is a critical link in improving patient outcomes and preventing hypoglycemic events. Unlike traditional continuous glucose monitoring (CGM), FGM can read glucose values in real time and display data and glucose trends for nearly 8 hours. It does not require fingertip blood correction during wear, can continuously monitor interstitial fluid glucose levels for 14 days, and form dynamic glucose profiles, making it convenient for clinical application.

The accuracy of FGM is particularly important for clinical work and has been validated in both animal and human studies, with clinical accuracy reaching 99%. However, in clinical practice, it can still be observed that FGM data from some patients differ significantly from actual venous blood glucose. Studies have shown that there is considerable individual variation in FGM accuracy, and the reasons remain inconclusive. FGM measures interstitial fluid glucose, and electrolyte ions, water, and other molecular substances are transferred between blood and interstitial fluid, which may affect the accuracy of FGM sensors. Additionally, research on the effects of certain body composition factors, such as body water, inorganic salt content, body fat mass, and subcutaneous fat thickness, on FGM accuracy is limited. Based on this, this study analyzed diabetic patients with poor FGM accuracy to explore the related influencing factors of FGM accuracy, aiming to provide a reference for clinical FGM application.

Methods

Study Subjects

Patients with type 2 diabetes mellitus (T2DM) hospitalized in the Department of Endocrinology of the Second Affiliated Hospital of Zhengzhou University in 2022 were selected as study subjects. Inclusion criteria were: (1) voluntary use of FGM; (2) clinical diagnosis of T2DM according to the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2020 Edition)". Exclusion criteria were: (1) severe liver or kidney function impairment; (2) sensor detachment or damage during the study; (3) inability to conduct venous blood glucose comparison as required; (4) severe emaciation and malnutrition; (5) inability to move independently or mobility restrictions; (6) severe infection, allergy, or major organ disease; (7) diabetic ketoacidosis; (8) MARD between 10% and 20%. Ultimately, 57 patients were included. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (approval number: 2021340). All patients provided informed consent.

Data Collection

General Data General data were collected through the electronic medical record system, including gender, age, height, weight, hyperuricemia, use of uric acid-lowering drugs, and BMI was calculated.

Blood Glucose Monitoring All enrolled patients used the hospital version FGM sensor (Freestyle LibreH®, Abbott). The same nursing staff inserted the sensor into the skin on the back of the patient's upper arm or lower triceps area according to the standard FGM sensor insertion procedure, then activated the sensor using a scanner to monitor blood glucose data for 14 days. At least one venous fasting blood glucose or 2-hour postprandial blood glucose comparison was performed during the early (days 2-4), middle (days 5-8), and late (days

8-12) sensor wear periods. When obtaining comparison blood glucose, venous blood was first drawn to measure venous blood glucose, followed by scanning to obtain FGM sensor blood glucose within 3-4 minutes. The venous blood glucose and corresponding FGM scan value were recorded as a pair, with each patient obtaining at least 3 pairs of values.

Body Composition Analysis Data Body composition analysis data were collected one day before FGM sensor insertion, strictly following the operating instructions of the Donghuayuan DBA-610 body composition analyzer. Patients were required to empty their bladder and bowels before measurement, and talking, moving, and eating were prohibited during measurement. After starting the machine and entering patient information, patients held the handles tightly with thumbs pressed against electrodes, stood barefoot on pedal electrodes, looked straight ahead, abducted both upper limbs by 15°, and naturally separated lower limbs. Data including total body water, extracellular fluid, protein, inorganic salts, body fat mass, muscle mass, BMI, waist-to-hip ratio, fat percentage, visceral fat area, basal metabolic rate, and fat mass, muscle mass, water mass, arm muscle circumference, and arm fat thickness of the arm where the probe was located were automatically obtained.

Hematological Parameters After 8-12 hours of fasting, 2-5 mL of venous blood was collected during the first venous blood glucose comparison to detect alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood potassium, blood sodium, blood chloride, blood calcium, blood phosphorus, glycated hemoglobin, hemoglobin (Hb), hematocrit (HCT), and estimated glomerular filtration rate (eGFR) was calculated.

eGFR Calculation eGFR was calculated using the Chinese modified simplified MDRD formula: eGFR = 175 × serum creatinine (mg/dL)^(-1.234) × age (years)^(-0.179) × gender (male = 1.00, female = 0.79).

Clarke Error Grid Analysis

Clarke error grid analysis was used to evaluate the clinical accuracy of FGM and assess the impact of measurement results on clinical treatment decisions. Zone A represents clinically accurate values (within $±$20% of venous glucose), where data in this region would lead to correct clinical decisions. Zone B represents clinically acceptable values (>20% difference from venous glucose), where treatment decisions based on these values remain clinically acceptable. Zones C, D, and E represent clinically erroneous zones where data are not referable and clinical decisions based on these data could lead to incorrect treatment. The more glucose values falling in Zones A and B, the higher the clinical accuracy of the detection method.

Grouping

Based on each patient's MARD for paired glucose values, the average MARD was calculated and patients were grouped. MARD is the average of absolute relative differences between all FGM values and corresponding venous glucose values, expressed as a percentage, used to evaluate FGM data accuracy. Studies have shown that sensors with MARD <10% have good measurement performance. MARD <10% was considered accurate FGM sensor precision (accurate group, n=23), while MARD >20% was considered inaccurate (inaccurate group, n=34).

Statistical Analysis

Clarke error grid analysis plotting was completed using MATLAB software (R2021a, MathWorks). SPSS 23.0 statistical software was used for data analysis. Normally distributed measurement data were expressed as ($\bar{x}\pm s$), and comparisons between two groups were performed using independent samples t-test. Count data were expressed as relative numbers, and comparisons between two groups were performed using ^{2} test or Fisher's exact test. Binary logistic regression was used to analyze influencing factors of FGM accuracy. P<0.05 was considered statistically significant.

Results

Clarke Error Grid Analysis Results

A total of 694 pairs of blood glucose data from 154 patients were collected. Using venous blood glucose as the reference value, Clarke error grid analysis of FGM scan values showed that 82.9% fell in Zone A, 16.9% in Zone B, 99.8% in Zone A+B, and 0.2% in Zone D, with an average MARD of 12.7% [Figure 1: see original paper].

Comparison of Baseline Data Between Two Groups

There were 23 patients in the accurate group (14 males, 9 females) and 34 in the inaccurate group (21 males, 13 females). The inaccurate group had higher MARD and muscle mass, and lower uric acid, body fat mass, and fat percentage compared with the accurate group (P<0.05). There were no statistically significant differences between the two groups in gender, age, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, blood urea nitrogen, creatinine, hyperuricemia, proportion taking uric acid-lowering drugs, eGFR, TC, TG, HDL-C, LDL-C, blood sodium, blood potassium, blood chloride, blood calcium, blood phosphorus, Hb, HCT, glycated hemoglobin, total water, extracellular fluid, protein, inorganic salts, BMI, waist-to-hip ratio, visceral fat area, arm fat mass, arm muscle mass, arm water mass, arm muscle circumference, or basal metabolic rate (P>0.05) .

Comparison of Baseline Data Between Two Groups by Gender

In male patients, the inaccurate group had lower uric acid, body fat mass, and fat percentage, and higher MARD and muscle mass compared with the accurate group ($P<0.05$). There were no statistically significant differences in age, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, blood urea nitrogen, creatinine, hyperuricemia, proportion taking uric acid-lowering drugs, eGFR, TC, TG, HDL-C, LDL-C, blood sodium, blood potassium, blood chloride, blood calcium, blood phosphorus, Hb, HCT, glycated hemoglobin, total water, extracellular fluid, protein, inorganic salts, BMI, waist-to-hip ratio, visceral fat area, arm fat mass, arm muscle mass, arm water mass, arm muscle circumference, or basal metabolic rate ($P>0.05$). In female patients, the inaccurate group had higher MARD compared with the accurate group ($P<0.05$), with no statistically significant differences in other indicators .

Binary Regression Analysis of Factors Influencing FGM Accuracy

Using FGM sensor accuracy (inaccurate=0, accurate=1) as the dependent variable and statistically significant results from Table 1 (uric acid, body fat mass, muscle mass, fat percentage, all assigned as actual values) as independent variables, binary logistic regression analysis showed that muscle mass and blood uric acid concentration were influencing factors of FGM accuracy ($P<0.05$) .

Further analysis using male FGM sensor accuracy (inaccurate=0, accurate=1) as the dependent variable and uric acid, body fat mass, muscle mass, and fat percentage (all assigned as actual values) as independent variables showed that muscle mass and blood uric acid concentration were influencing factors of FGM accuracy in male patients ($P<0.05$) .

Discussion

Due to the limitations of self-monitoring of blood glucose (SMBG), CGM has gradually become an extremely important component of diabetes management. The FGM launched in China in 2016 has both retrospective and real-time CGM functions, can continuously monitor interstitial fluid glucose levels for 14 days to form dynamic glucose profiles, and does not require fingertip blood correction during wear, making clinical blood glucose monitoring more convenient. FGM measures interstitial fluid glucose, which has a certain lag compared with venous blood glucose values. Studies have shown that the average lag time of interstitial fluid glucose in Chinese Han population is 3.1 minutes. Therefore, this study chose to scan and record FGM glucose values within 3-4 minutes after venous blood draw, and blood glucose accuracy on the first day of sensor wear is generally not high, so no blood glucose comparison was performed on day 1.

CORRADINI et al. evaluated the accuracy of FGM in a diabetic dog model, where 10 insulin-treated diabetic dogs were monitored using FGM for 14 days, showing clinical accuracy of 93%, 99%, and 99% at low, normal, and high glucose concentrations, respectively. BAILEY et al. conducted a prospective study

comparing FGM with SMBG and plasma glucose concentration, finding that FGM clinical accuracy was 99.0% compared with SMBG and 98.9% compared with venous blood samples. The Clarke error grid analysis results of this study showed that overall FGM accuracy is reliable (99.8% in Zone A+B), meeting international standards (ISO 15197:2013), although some individual patients still showed large differences between FGM glucose and venous glucose.

Previous studies have shown that FGM accuracy is not affected by factors such as age and BMI, and that changes in glucagon, free fatty acids, β-hydroxybutyrate, and lactate caused by physical exercise and food intake have no effect on sensor performance. Sensor accuracy is also not significantly related to wearing on the abdomen versus the arm. Our research group hypothesized that certain blood components and body composition might affect FGM sensor accuracy. Previous studies have shown that sensor accuracy is affected by HCT and concentrations of uric acid and bilirubin in blood samples. This study used an automatic biochemical analyzer to detect blood components and bioelectrical impedance analysis (BIA) for body composition measurement. Currently, BIA is the most widely used and reliable method for measuring body composition, utilizing differences in water content and electrical conductivity of different tissues to measure body water content, inorganic salt content, muscle mass, and body fat mass, among other components, to analyze the correlation between body composition and FGM sensor accuracy.

This study shows that sensor accuracy is not affected by electrolyte ions and other biochemical molecules in blood, nor by factors such as body water mass, fat content, inorganic salt content, and fat thickness at the sensor wearing site. However, FGM sensor accuracy is related to uric acid level and muscle mass in blood samples, with uric acid being a protective factor. Previous studies have shown that uric acid is an interfering factor affecting dynamic glucose sensor measurement results, possibly because patients with high uric acid are more likely to have metabolic disorders and obesity, with potentially thicker subcutaneous fat layers and higher sensor accuracy. This may be inconsistent with previous research results, but could also be related to bias caused by the small sample size in this study. Human muscle mass is an interfering factor for FGM accuracy. Increased muscle mass, especially in overweight muscular individuals, may reduce subcutaneous fat layer thickness, bringing the sensor closer to underlying muscle tissue where glucose concentration may be more lagging, thereby impairing FGM sensor accuracy. However, this study did not find a correlation between body fat mass and fat percentage with sensor accuracy, possibly because diabetic patients are generally centrally obese, and the specific reasons require further investigation.

Notably, due to differences in muscle mass and body fat mass between males and females, this study further conducted intergroup comparisons and correlation analyses in different genders. The results showed no statistically significant differences in various indicators between accurate and inaccurate groups in female patients, suggesting that factors causing FGM sensor inaccuracy in females

may not be among the indicators included in this study and require further exploration. Factors related to FGM sensor accuracy may be mainly related to intergroup differences in male patients.

This study has several limitations. First, the sample size is relatively small, which may lead to bias in the results. Second, there were too few factors with intergroup differences in the original data of the two groups, which is disadvantageous for studying sensor accuracy.

In conclusion, the overall accuracy of FGM sensors is reliable, but large differences may occur in individual patients, which may be related to blood uric acid concentration and increased muscle mass. The effects of uric acid and muscle mass on sensor accuracy are mainly observed in males, while other undiscovered factors may exist in females.

Author Contributions: CHU Xiaojing and LI Jun proposed the main research objectives, responsible for study conception and design, and implementation; FU Yanqin provided administrative support for the entire study; CHU Xiaojing, LIU Danqing, and LIU Aiping collected and organized data; LI Jun and ZHANG Yuanyuan performed statistical processing, figure and table preparation and presentation; all authors participated in manuscript writing; LI Jun and FU Yanqin were responsible for quality control and review of the article, overall responsibility, and supervision.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.