

Association of continuous glucose monitoring-derived time in range with major amputation risk in diabetic foot osteomyelitis patients undergoing amputation

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Abstract

Objective: The metrics generated from continuous glucose monitoring (CGM), such as time in range (TIR), are strongly correlated with diabetes complications. This study explored the association of perioperative CGM-derived metrics with major amputation risk in patients with diabetic foot osteomyelitis (DFO).

Methods: This study recruited 55 DFO patients with grade 3–4 wounds according to the Wagner Diabetic Foot Ulcer Classification System, all of whom underwent CGM for 5 days during the perioperative period. The CGM-derived metrics were defined in accordance with the most recent international consensus recommendations.

Results: Patients with major amputation had significantly less TIR and higher time below range (TBR) (all $p < 0.05$). In binary logistic regression analyses, a lower TIR was associated with the risk of major amputation (odds ratio: 0.83 [95% confidence interval: 0.71–0.99], $p = 0.039$). This association remained statistically significant after adjustments for age, sex, body mass index, type of diabetes, smoking, drinking, durations of diabetes and DFU, ankle-brachial index, albumin, estimated-glomerular filtration rate, Society for Vascular Surgery wound, ischemia, and foot infection (WIFI) stage, multidrug-resistant organisms, and hemoglobin A1c. Further adjustment for the mean amplitude of glycemic excursion (MAGE) reduced this association. TBR was also independently associated with the risk of major amputation (odds ratio: 1.60 [95% confidence interval: 1.17–2.18], $p = 0.003$); this association persisted after adjustment for MAGE.

Conclusion: Perioperative TIR (3.9–10.0 mmol/L) and TBR (<3.9 mmol/L) were significantly associated with major amputation in hospitalized patients with DFO.

Keywords: continuous glucose monitoring, diabetic foot osteomyelitis, major amputation, time in range

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Introduction

According to the International Diabetes Federation, approximately 463 million adults worldwide were living with diabetes mellitus (DM) in 2019. This total number is predicted to rise to more than 700 million by 2045.¹ Diabetic foot ulcer (DFU) is one of the most common and serious

complications of diabetes; its lifetime risk can reach 34%.² At least 50% of DFUs are complicated by infection upon presentation.^{3,4} Diabetic foot osteomyelitis (DFO) is a moderate to severe infection associated with DFU; it occurs in 40–80% of infected ulcer and leads to gangrene and limb amputation.⁵ The mortality rate is much

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higher in patients with DFO than in the patients with DFU.⁶ Considering the higher prevalence, rates of disability and mortality in affected patients, DFO has increased diabetes-related costs for patients, their families, and society.

Diabetic patients have increased susceptibility to various types of infectious diseases such as DFO, particularly when blood glucose control is poor.^{7,8} Therefore, it is important to elucidate the effects of optimal glycemic management on surgical treatment in DFO patients. Hemoglobin A1c (HbA1c) is a “gold standard” for glycemic management⁹; improvement of HbA1c considerably slows the development of diabetes-related macrovascular and microvascular complications.^{10,11} However, there are important limitations regarding HbA1c, such as the use of varied testing methods and lack of information concerning individual glycemic status patterns.^{12,13} Continuous glucose monitoring (CGM) can provide direct data regarding glycemic excursions and daily glucose profiles, which can partially overcome the limitations of HbA1c assessment. Moreover, previous studies have shown that CGM more strongly increases the glycemic control benefit, compared with self-monitoring of blood glucose (SMBG) in type 1 diabetes (T1DM) and type 2 diabetes (T2DM) patients.^{14,15} Among the metrics derived from CGM, time in target range (TIR) is the simplest key indicator, which describes the percentage of time glucose values are within the target glucose range (usually 3.9–10 mmol/L) throughout the day. TIR has been proved strongly associated with the development of diabetic retinopathy, carotid intima-media thickness, albuminuria, and cardiovascular autonomic neuropathy in DM patients.^{16–20}

There are minor and major types of DFU-related amputation. DFO leads to minor or major amputations in almost 20% of patients.⁵ Major amputation leads to significant functional disability, increases cardiovascular disease, and worsens both quality of life and 5-year mortality, compared with minor amputation.^{21,22} Moon *et al.*²³ and Lu *et al.*²⁴ reported that high HbA1c had significantly associated with the risk of major amputation. Perioperative glucose fluctuation is a major detrimental risk factor for healing potential and surgical site infections in diabetic patients.^{25,26} Notably, Aragón-Sánchez and Lázaro-Martínez²⁷ found that perioperative glycemic control has

important effect on the outcomes of surgical treatment in patients with DFO. To our knowledge, no study has explored the impact of perioperative glycemic variability on the risk of major amputation.

Using data from a case–control retrospective study including patients with DFO with available CGM data during hospitalization, we evaluated the relationship between CGM-derived TIR and the rate of major amputation.

Methods

Study population

In total, 55 patients with DFO, all of whom underwent any amputation from March to December in 2019, were consecutively recruited from among hospitalized patients in our department. Osteomyelitis was diagnosed according to probing-to-bone test results, laboratory test findings (including white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and hypersensitive C-reactive protein (CRP)) and radiological studies of the foot. Data were collected regarding each patients’ medical history including type of diabetes, durations of DM and DFU, smoking, drinking, hypertension, coronary artery disease, and stroke. Exclusion criteria were age <18 years; pregnancy; diabetic ketoacidosis or hyperglycemic hyperosmolar state; chronic diseases in the end stage, which deteriorated gradually and could not be improved (e.g., severe kidney or liver dysfunction, terminal malignant tumors, mental disorders); grades 1–2 or 5 wounds according to the Wagner Ulcer Classification System; recurrent hypoglycemic events or hypoglycemia unawareness on current therapy; noncompliance.

CGM parameters

During the perioperative period, a retrospective CGM system (Medtronic Inc., Northridge, CA, USA) was used to monitor glycemia for five consecutive days, including the day of surgery, and 2 days before and after operation. At least four capillary blood glucose measurements per day were obtained with a glucometer (OneTouch® Ultra®, Johnson & Johnson, New Brunswick, NJ, USA) to calibrate each CGM trace. After the 5-day monitoring period, we calculated the TIR, the time above target range (TAR), the time below

target range (TBR), and the mean amplitude of glycemic excursion (MAGE) to assess glycemic control. TIR, glucose 3.9–10.0 mmol/L, was computed by calculating the percentage of time spent in target range during a 24 h period. TAR (>10.0 mmol/L) and TBR (<3.9 mmol/L) were calculated in a similar manner; MAGE was determined by calculating the arithmetic mean of the differences between peaks and nadirs, and only the amplitudes of more than one standard deviation (SD) of the mean glucose were considered.

Anthropometric and laboratory measurements

Physical examinations included measurements of height, weight, and blood pressure were collected by trained doctors. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. One day before the CGM monitoring period, venous blood samples were collected after an overnight fast. Ankle-brachial index (ABI) measurements were performed using an 8-MHz Doppler probe (Vista AVS; Summit Doppler Systems, Inc., Golden, CO, USA). ABI was calculated as the ratio of the highest ankle systolic blood pressure to the highest brachial pressure.

Serum glucose concentrations, creatinine (Scr), albumin, and CRP were determined using an auto-analyzer (Beckman Coulter, Brea, CA, USA). HbA1c was assayed by high-performance liquid chromatography with a hemoglobin testing system (Bio-Rad, Hercules, CA, USA). WBC and hemoglobin (Hb) levels were measured by an automatic blood analyzer (Beckman Coulter). ESR was determined using a fully automated ESR analyzer Monitor-100 (Vital Diagnostics, Forli, Italy). Albuminuria levels were measured using a turbidimetry assay (Maccura Biotechnology Co. Sichuan, China). Estimated-glomerular filtration rate (eGFR) was calculated according to the modified glomerular filtration rate estimating equation for Chinese patients [eGFR (ml/min/1.73 m²) = 175*Scr^{1.234}*age^{-0.179}*0.79 (if female)].

Definitions of diabetic complications

The presence of diabetic neuropathy (DPN) was determined by an objective neurological examination that included electrophysiological tests

performed by a trained physiatrist with a Synergy electromyograph machine (Keypoint; Dantec Dynamics A/S, Denmark), vibration perception threshold (VPT) assayed with a biothesiometer—vibrometer-VPT (Beijing Laxons Technology Co., Ltd., China), and 10 g monofilament sensation. Diabetic retinopathy (DR) was determined *via* retinal fundus photographs using a nonmydriatic camera (Nonmyd; Kowa Company, Ltd., Osaka, Japan). The diagnosis of diabetic nephropathy (DN) was based on an albuminuria ≥ 30 mg/g creatinine and/or an eGFR < 160 ml/min/1.73 m².²⁸

Ulcers severity assessment and intervention

Relevant ulcers were assessed and recorded on admission. The Wagner Ulcer Classification System and the Society for Vascular Surgery wound, ischemia, and foot infection (WIFI) Classification System were utilized for wound staging.^{29,30} Multidrug-resistant organisms (MDROs) were defined according to an International Expert Proposal.³¹ Major amputation was defined as amputation above the ankle level. All patients received standard wound intervention that included debridement and tissue cultures of infected wounds. Empirical antibiotics were used in the first 3 days; subsequently, organism-specific antibiotics were used. Other interventions included glycemic control, wound dressing, and negative pressure assisted closure (if necessary).

Statistical analyses

Sample characteristics were expressed as means ± SD for normally distributed continuous data, medians (interquartile ranges) for continuous data with skewed distributions, and frequencies (percentages) for categorical variables. Trends of demographic characteristics between groups were compared using Student's *t* test for normally distributed variables and the Mann-Whitney *U*-test for non-normally distributed variables. Pearson's chi-squared test was used to compare differences for categorical variables. Binary logistic regression was used to assess the relationships of 5% increases in TIR, TAR, and TBR with the risk of major amputation, after adjustment for potential covariates (e.g., age, sex, cigarette smoking, drinking, BMI, DM type, DM duration, DFU duration, ABI, albumin, eGFR, WIFI stage, MDROs, HbA1c, and MAGE). The

aforementioned statistical tests were performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Two tailed p values < 0.05 were considered statistically significant.

Results

General characteristics

In total, 55 DFO patients whom underwent any amputation were included in this study, of whom 20 (36.4%) had a major amputation. Clinical characteristics are shown in Table 1. The mean age of all patients was 68.29 ± 8.48 years, and 69.1% were males. The durations of DM and DFU were 72.00 (60.00–132.00) months and 6.23 ± 2.43 months in patients with minor amputation, and 75.50 (56.25–118.00) months and 7.85 ± 1.66 months in patients with major amputation, respectively. The prevalence of T2DM was 88.6% in patients with minor amputation, and 85% in patients with major amputation. Patients with major amputations had longer DFU duration; lower albumin, ABI, TIR; and higher TBR.

CGM target achievement according to major amputations

The rates of achieving CGM targets according to major amputation status are shown in Figure 1. The targets were selected in accordance with the recent Advanced Technologies & Treatments for Diabetes (ATTD) consensus recommendations.³² When compared with study patients who underwent minor amputations, patients with major amputations had significantly lower rates of

achieving, the targets of TIR $> 50\%$, TAR $< 50\%$, and TBR $< 1\%$ among older and/or high-risk individuals with DM.

Associations of CGM parameters with the risk of major amputation

Table 2 shows the association of major amputation with CGM core metrics, including TIR, TAR, and TBR. The odds ratio (OR) for the presence of major amputation was 0.83 [95% confidence interval (CI): 0.71–0.99] per 5% increase in a TIR 3.9–10.0 mmol/L. After further adjustments for age, sex, BMI, type of DM, smoking, and drinking (Table 2, Model 2); durations of diabetes and DFU (Model 3); ABI, albumin, eGFR, Wifi stage, MDROs (Model 4); and HbA1c (Model 5), the association remained significant. However, the association between TIR and major amputation was not statistically significant in the model adjusted for MAGE (Model 6). TBR was significantly associated with the risk of major amputation; this association persisted after adjustment for MAGE (Model 6). Conversely, TAR was not significantly associated with the risk of major amputation. With further adjustments for confounders mentioned above, estimates of association were similar.

Discussion

To our knowledge, this study is the first to report a significant inverse association between a CGM-derived TIR 3.9–10.0 mmol/L and the risk of major amputation in hospitalized patients with DFO. This association was maintained despite adjustments for various clinical risk factors,

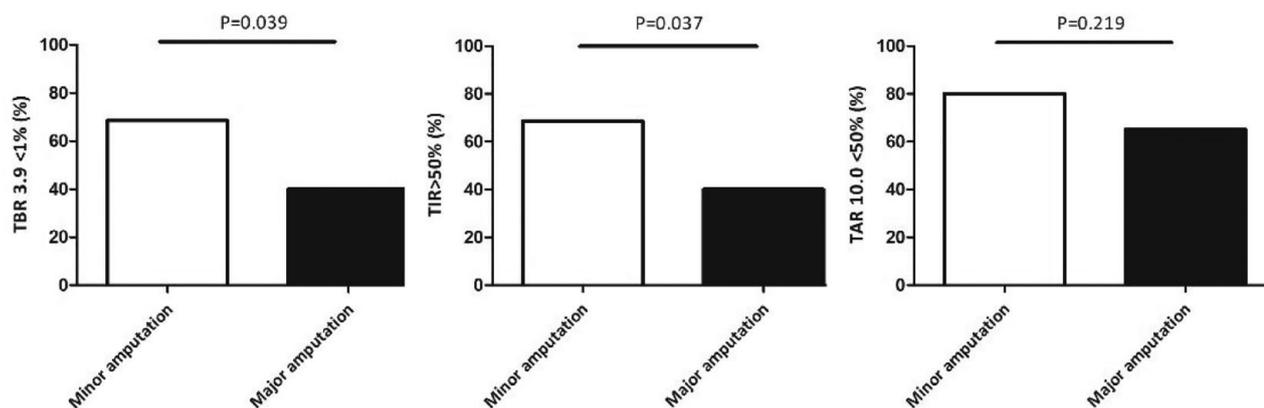


Figure 1. Prevalence of subjects who achieved the CGM targets according to the presence of major amputation.

Table 1. Characteristics according to the presence of major amputation.

| | Total | Minor amputation | Major amputation | <i>p</i> value |
|------------------------------------|----------------------|----------------------|----------------------|----------------|
| Age (years) | 68.29 ± 8.48 | 68.74 ± 7.77 | 67.50 ± 9.76 | 0.606 |
| Male, <i>n</i> (%) | 38 (69.1) | 25 (71.4) | 13 (65.0) | 0.620 |
| Current smoker, <i>n</i> (%) | 27 (49.1) | 21 (60.0) | 8 (40.0) | 0.153 |
| Alcohol drinker, <i>n</i> (%) | 21(38.2) | 15 (42.9) | 6 (30.0) | 0.345 |
| T2DM, <i>n</i> (%) | 48 (87.3) | 31 (88.6) | 17 (85.0) | 0.702 |
| History of CAD, <i>n</i> (%) | 25 (45.5) | 17 (48.6) | 8 (40.0) | 0.539 |
| History of stroke, <i>n</i> (%) | 14 (25.5) | 7 (20.0) | 7 (35.0) | 0.219 |
| Duration of DM (months) | 72.00 (60.00–120.00) | 72.00 (60.00–132.00) | 75.50 (56.25–118.00) | 0.752 |
| Duration of DFU (months) | 6.82 ± 2.30 | 6.23 ± 2.43 | 7.85 ± 1.66 | 0.011 |
| Wagner stage | | | | 0.064 |
| 3 (%) | 31 (56.4) | 23 (65.7) | 8 (40) | |
| 4 (%) | 24 (43.6) | 12 (34.3) | 12 (60) | |
| Wifi stage | | | | 0.592 |
| 3 (%) | 19 (34.5) | 13 (37.1) | 6 (30) | |
| 4 (%) | 36 (65.5) | 22 (62.9) | 14 (70) | |
| MDROs (%) | 19 (34.5) | 13 (37.1) | 6 (30.0) | 0.592 |
| DPN, <i>n</i> (%) | 48 (87.3) | 30 (85.7) | 18 (90.0) | 0.646 |
| DN, <i>n</i> (%) | 33 (60.0) | 21 (60.0) | 12 (60.0) | 1.000 |
| DR, <i>n</i> (%) | 31 (56.4) | 21 (60.0) | 10 (50.0) | 0.472 |
| BMI (kg/m ²) | 25.48 ± 4.24 | 25.95 ± 4.22 | 24.66 ± 4.25 | 0.280 |
| Hb (g/L) | 84.20 ± 19.77 | 83.00 ± 20.00 | 86.30 ± 19.70 | 0.556 |
| HbA1c (%) | 7.86 ± 1.66 | 8.11 ± 1.77 | 7.41 ± 1.36 | 0.132 |
| WBCs (10 ⁵ /L) | 9.20 (6.60–12.90) | 9.60 (7.20–13.10) | 7.40 (5.75–12.90) | 0.298 |
| CRP (mg/L) | 49.30 (32.10–93.20) | 49.30 (31.40–93.20) | 46.10 (32.63–94.13) | 0.993 |
| ESR (mm/h) | 51.00 (44.00–75.00) | 57.00 (44.00–75.00) | 46.50 (44.00–75.75) | 0.511 |
| eGFR (ml/min/1.73 m ²) | 57.90 (45.20–77.30) | 55.40 (45.30–77.50) | 60.50 (37.70–77.25) | 0.854 |
| Albumin (g/L) | 28.95 ± 9.86 | 28.54 ± 9.24 | 29.65 ± 11.06 | 0.692 |
| ABI | 0.77 ± 0.16 | 0.70 ± 0.18 | 0.59 ± 0.10 | 0.013 |
| MAGE (mmol/L) | 4.20 ± 1.87 | 3.90 ± 1.82 | 4.74 ± 1.87 | 0.110 |
| TBR (%) | 0 (0–13.00) | 0 (0–7.00) | 12.50 (0–26.50) | 0.005 |
| TIR (%) | 56.20 ± 17.55 | 59.97 ± 16.54 | 49.60 ± 17.71 | 0.034 |
| TAR (%) | 36.62 ± 17.83 | 36.31 ± 16.57 | 37.15 ± 20.28 | 0.869 |

Continuous variables are expressed as means ± SD and median with interquartile range; categorical parameters are presented as counts, with percentages in parentheses, *n* (%).
 ABI, ankle-brachial index; BMI, body mass index; CAD, coronary artery disease; CRP hypersensitive C-reactive protein; DFU, diabetic foot ulcer; DM, diabetes mellitus; DN, diabetic nephropathy; DPN, diabetic neuropathy; DR, diabetes retinopathy; ESR, erythrocyte sedimentation rate; eGFR, estimated-glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; MAGE, mean amplitude of glycemic excursions; MDROs, multidrug-resistant organisms; TAR, time above range; TBR, time below range; TIR, time in range; T2DM, type-2 diabetes mellitus; WBC, white blood cell; Wifi, Society for Vascular Surgery wound, ischemia, and foot infection.

Table 2. Association between CGM-derived metrics and the presence of major amputation.

| CGM metrics | | Odds ratio (95% CI) | p value |
|-------------|---------|---------------------|---------|
| TIR | Model 1 | 0.83 (0.71–0.99) | 0.039 |
| | Model 2 | 0.81 (0.71–0.98) | 0.036 |
| | Model 3 | 0.79 (0.71–0.97) | 0.027 |
| | Model 4 | 0.95 (0.91–0.99) | 0.046 |
| | Model 5 | 0.95 (0.90–0.99) | 0.044 |
| | Model 6 | 0.96 (0.92–1.02) | 0.161 |
| TAR | Model 1 | 1.01 (0.87–1.18) | 0.866 |
| | Model 2 | 1.01 (0.86–1.20) | 0.871 |
| | Model 3 | 1.03 (0.86–1.24) | 0.739 |
| | Model 4 | 1.01 (0.97–1.05) | 0.745 |
| | Model 5 | 1.01 (0.97–1.05) | 0.715 |
| | Model 6 | 1.00 (0.95–1.05) | 0.966 |
| TBR | Model 1 | 1.60 (1.17–2.18) | 0.003 |
| | Model 2 | 1.78 (1.20–2.63) | 0.004 |
| | Model 3 | 1.84 (1.19–2.85) | 0.006 |
| | Model 4 | 1.12 (1.01–1.24) | 0.021 |
| | Model 5 | 1.13 (1.02–1.24) | 0.020 |
| | Model 6 | 1.11 (1.01–1.23) | 0.048 |

Odds ratios represent per 5% increase in TIR, TAR, and TBR.
 Model 1: unadjusted
 Model 2: adjusted for age, gender, BMI, type of DM, smoking, and drinking
 Model 3: adjusted for model 2 plus duration of diabetes and DFU
 Model 4: adjusted for model 3 plus ABI, albumin, eGFR, Wlfi stage, and MDROs
 Model 5: adjusted for model 4 plus HbA1c
 Model 6: adjusted for model 4 plus MAGE
 ABI, ankle-brachial index; BMI, body mass index; DFU, diabetic foot ulcer; DM, diabetes mellitus; eGFR, estimated-glomerular filtration rate; HbA1c, hemoglobin A1c; MAGE, mean amplitude of glycemic excursions; MDROs, multidrug-resistant organisms; TAR, time above range; TBR, time below range; TIR, time in range; Wlfi, Society for Vascular Surgery wound, ischemia, and foot infection.

including HbA1c. It is notable that adjustment for MAGE reduced the association of TIR with the risk of major amputation. In addition, an increase in the amount of TBR < 3.9 mmol/L, a

marker of hypoglycemia, was also independently associated with major amputation; this relationship was not observed for TAR.

According to the global lower Extremity Amputation Study Group, 25%–90% of all amputations are associated with DM.³³ HbA1c is currently the most well-known standard for assessing glycemic control; improvements in HbA1c greatly reduce the development of diabetic complications. Previous studies have analyzed the relationships of HbA1c with DFO outcomes. Moon *et al.*²³ and Lu *et al.*²⁴ found that HbA1c was associated with major amputation risk. However, Peters *et al.*³⁴ and Aragon-Sanchez *et al.*²⁷ demonstrated that HbA1c is not useful for predicting foot infection risk and DFO outcomes. Our data did not show a significant relationship between HbA1c and major amputations risk. The discrepancy might be explained by differences in the selection of study participants, who were restricted to patients with ulcer grade 3–4 in this study.

There are also some limitations concerning the use of HbA1c as the sole marker of glycemic management, which reflects more chronic sustained dysglycemia, rather than an acute condition. Perioperative glycemic control, which is not closely reflected by HbA1c, is a predictive factor for amputation and surgical site infections in DFU patients.^{26,27} Xie *et al.*³⁵ recently found that TIR, assayed by 7-point glucose testing, has detrimental effects on amputation and all-cause mortality in hospitalized patients with DFUs. CGM, a novel methodology that provides all glucose data for a particular time frame and represents the variability of glucose excursions, could help to resolve some of the limitations concerning HbA1c and SMBG. In our study, CGM-derived TIR during the preoperative period was inversely associated with major amputation risk, despite further adjustment for HbA1c. This suggests the value of TIR in predicting major amputation risk independent of HbA1c. However, the discrepancy between the TIR value and the major amputation risk progressively deteriorated after adjustment for MAGE, a typical measure of glycemic variability, which showed no significant difference between minor and major amputation group. A possible cause could be the negative correlation between TIR and MAGE in our study ($r = -0.321$; $p = 0.017$; data not shown), which might have led to multicollinearity in the logistic regression model and thus affected the results. Nevertheless, our study provides evidence

regarding the effects of TIR on the risk of major amputation in patients with DFO.

Hypoglycemia is the most common acute complication in T1DM and may also occur in T2DM patients who are receiving insulin or insulin secretagogues therapy,³⁶ which have been associated with risks of diabetes complications, short- and long-term morbidity. Peled *et al.*³⁷ demonstrated that inpatient hypoglycemia was an independent risk factor for any and major amputations. SMBG, used to confirm hypoglycemia, generally misses asymptomatic hypoglycemia. Conversely, the use of CGM provides more detailed insights concerning hypoglycemia exposure in DM patients. Our study showed that TBR has an independent association with major amputation risk in patients with DFO, despite adjustment for the HbA1c or MAGE.

The strengths of our study are that it is the first study to analyze the relationships of CGM-derived TIR and other metrics with the risk of major amputation in patients with DFO. In addition, we referenced a recently published ATTD consensus recommendations for assessing the proportion of patients who met the glycemic target for TIR, TAR, and TBR. However, several limitations of our study should be noted. First, all patients in our study were enrolled from one hospital and the sample size was small, leading to potential selection bias. Second, the CGM monitoring period in our study was 5 days, rather than the recommended 14 days, which may have been insufficient to record appropriate glycemic control in our patients. Third, in this study, we chose a retrospective CGM system, which could not offer prompt feedback and optional alarm against hypoglycemia and hyperglycemia to the clinicians. Further studies with real-time CGM device are needed to clarify the relationship of more real-time and appropriate treatment decisions with outcome of DFO patients. Fourth, this was a cross-sectional observational investigation; thus, we could not elucidate the causal relationships of CGM-derived metrics with major amputation risk. Further multicenter, large scale, longitudinal studies are needed.

Our study supports that CGM-derived TIR and TBR, as potential tool for predicting the risk of major amputation risk in patients with DFO; these relationships are independent of HbA1c. Therefore, it is crucial to minimize the glycemic fluctuation and hypoglycemia in DFO patients,

especially during the perioperative period, which can effectively reduce the disability rate and improve the quality of life.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Sir Run Run Shaw Hospital (ZJU20170252) and was conducted in accordance with the 1964 Helsinki Declaration.

Consent for publication

Written informed consent to participate was obtained from all patients.

Author contribution(s)

Xueyao Yin: Funding acquisition; Writing—original draft.

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Chao Liu: Project administration; Writing—review & editing.

Huilan Yao: Data curation; Software.

Jiaxing You: Formal analysis; Methodology.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding authors on reasonable request.

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