Glycemic Variability as a Predictor of Graft Failure Following Infrainguinal Bypass for Peripheral Arterial Disease: A Retrospective Cohort Study

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Background: Glycemic variability (GV), measured as the change in visit-to-visit glycated hemoglobin (HbA_{1c}), increases the risk of multiple adverse outcomes. However, the impact of GV on graft patency following infrainguinal bypass (IIB) is unknown. A retrospective cohort study was undertaken to assess the impact of GV on graft patency.

Methods: A 3-year single-center retrospective case notes analysis of all people undergoing IIB between 2017 and 2019. Rutherford stage, graft conduit, level of bypass, procedure details, baseline demographics, comorbidities, and GV were assessed. Time to reintervention, ipsilateral amputation, or death was recorded to determine primary patency (PP).

Results: One hundred six IIB outcomes were analyzed: mean (± standard deviation) age 68.0 (9.2) years; 69 (65.1%) male, 37 (33.9%), 75 (70.8%) had diabetes mellitus; and 46 (43.4%) underwent elective procedures. GV $>$ 9.1% was associated with significantly lower median PP than GV $<$ 9.1%, 198 (97−753.5) vs. 713 (166.5−1,044.5) days ($P = 0.045$). On univariate analysis, GV $>$ 9.1% vs. $<$ 9.1% was significantly associated with PP (hazard ratio [HR] 1.85 [confidence interval {CI} 1.091−3.136], $P = 0.022$). Bypass level was also a univariate predictor, with below knee bypasses (HR 2.31 [CI 1.164−4.564], $P = 0.017$), and tibial (HR 2.00 [CI 1.022−3.090], $P < 0.043$) having lower PP than above knee bypasses. On multivariate adjustment, GV $>$ 9.1% and level of bypass remained independent predictors of PP, HR 1.96 (95% CI: 1.12−3.42, $P = 0.018$) and HR 2.54 (95% CI: 1.24−5.22, $P = 0.011$), respectively.

Conclusions: GV is an independent predictor of PP following infrainguinal bypass, thus optimizing GV should be a therapeutic target.

INTRODUCTION

Diabetes mellitus (DM) is a well-established risk factor for peripheral arterial disease (PAD). For people with diabetes, PAD is the most common cause of amputations.[1] Furthermore, it has been reported that people with better glycated hemoglobin (HbA_{1c}) at baseline have better survival than those with more

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lenient control.[2] Currently, mean HbA_{1c} is the gold standard measure of glycemic control before surgery. The Center of Perioperative Care guidelines suggest the optimum preoperative HbA_{1c} is <69 mmol/mol.[3]

Glycemic variability (GV) is a novel way to measure glycemic control.[4] Short-term GV is the fluctuation during or between days (usually measured by blood glucose measurements), and long-term GV is the fluctuation over weeks and months (usually assessed by HbA_{1c}).[5] GV might be an additional or better predictor of complications of diabetes than mean HbA_{1c}.[6–8] Understanding the mechanisms, homeostasis, and role of GV in macrovascular and microvascular complications are important in considering targeted measures to manage diabetes-related complications.[9] The effects of long-term HbA_{1c} variability on mortality,[8,10–13] microvascular and macrovascular complications,[8,10,14] cardiovascular complications,[11,15–17] and the healing of diabetic foot ulcers[18] have been demonstrated.

Few studies have investigated the role of long-term GV in prediction of adverse postoperative outcomes and it remains unknown if GV affects outcomes in those undergoing bypass surgery. This study aims to investigate whether HbA_{1c} and its long-term variability preoperatively influences outcomes following infrainguinal bypass for PAD.

METHODS

This was a single-center retrospective, observational cohort study of all people undergoing infrainguinal bypass for PAD between January 1, 2017 and December 31, 2019 at our institution. Patients undergoing exclusion bypasses of popliteal aneurysms or other intrinsic vascular wall abnormalities were excluded, as were those who were lost to follow-up or with insufficient demographic details.

Baseline demographics were collected using patient clinical records, and any previous ipsilateral endovascular or open surgical interventions were recorded. Demographic data comprised of age at procedure, sex, smoking status (current smoker, ex-smoker, never smoker), and comorbidities (chronic obstructive pulmonary disease, hypertension, ischemic heart disease [IHD], cerebrovascular disease, DM). We also collected data on Rutherford stage at operation, procedures performed under an elective versus nonelective pathway (including emergency and urgent operations), procedure site, graft conduit (composite, vein, or prosthetic), length of hospital stay, and graft patency at discharge. Preoperative hemoglobin (Hb) and creatine values were also collected. However, no univariate associations were found and so these were not entered into the multivariate models.

Subjects were followed up until ipsilateral major limb amputation, death or December 31, 2021, giving a minimum follow-up period of 2 years. Latest follow-up (last graft surveillance scan or postbypass clinic review), graft patency, and any postoperative endovascular or open surgical interventions were reported on. Our institution has no standardized follow-up protocol following IIB, with variability between consultant practice. However, patients were encouraged to contact the vascular department if they developed any new vascular symptoms as standard. Therefore, we assumed that if there were no new referrals on the outpatient referral console, no new clinical letters or admissions for postoperative intervention that the bypass graft had remained patent at the end of the study period.

For all individuals, up to 5 HbA_{1c} results were recorded for the 5 years prior to bypass or until January 1, 2012. All HbA_{1c} observations recorded were at least 30 days after their previous HbA_{1c}. We recorded the closest preoperative and postoperative HbA_{1c} result. Those with 3 or more results had preoperative HbA_{1c} variability determined using the standard deviation (SD) of these results, as previously done by Dhatariya et al.[18] Further HbA_{1c} variability analysis was done by splitting the SD of HbA_{1c} into quartiles, similar to methods in previous work.[18,19] With HbA_{1c} SDs split into quartiles, the worst quartile (>9.1% SD) was compared to the rest (<9.1% SD). Therefore, higher GV was measured as >9.1% versus lower GV as <9.1%.

Because this was a retrospective analysis study, our audit department confirmed that ethical approval was not necessary given the observational nature of this retrospective study and the use of pseudo-anonymized data.

Outcomes

The main outcome assessed was GV given the lack of previous research on the effect of GV in infrainguinal bypass outcomes. We assessed the effect of GV on primary patency (PP), secondary patency (SP), and amputation-free survival. PP was measured by time in days from procedure to reintervention (angioplasty, endarterectomy, or bypass), graft blockage (as determined by consultant diagnosis or radiological confirmation), or amputation. SP was time in days from procedure to final blockage (that received no subsequent intervention) or amputation. We appreciate that rarely amputations are performed due to sepsis with a patent graft but we could not find any evidence of this in the hospital records.

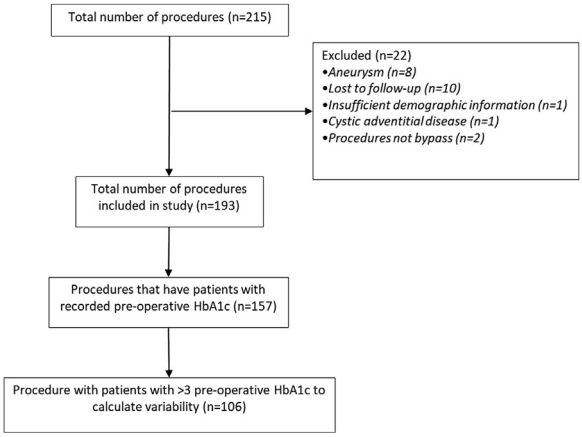

Fig. 1. Consort diagram showing cohort selection process.

Amputation-free survival was time in days from procedure until ipsilateral amputation or death.

Statistical Methods

Descriptive statistics were presented as absolute number with percentages or mean with SD. A survival analysis was performed on PP (as well as SP, and amputation-free survival) to explore if HbA_{1c} variability was associated with PP.

A Cox Proportional Hazards model for PP has been used to adjust for smoking, IHD, elective or emergency surgery, Rutherford scores, and type of bypass. Unadjusted and adjusted odds ratios and their respective 95% confidence interval (CI) have been reported. There were only 5 potential confounding factors that could be included in the model: smoking, IHD, elective or emergency surgery, Rutherford scores, and type of bypass; all of which were significant except smoking and IHD. It was decided to include all factors irrespective of whether they were significant in the univariate analysis, to understand if they had any confounding effect with GV and the primary outcome of PP, the secondary objectives of SP, and amputation-free survival.

There was a very strong correlation between diabetes status and GV; for this reason, the GV model excluded diabetes status. The model was repeated including diabetes status and excluding GV.

To avoid collinearity, data exploration was performed to assess if there were any associations or correlations between factors. If there were any strong associations between factors, separate models would be conducted.

Results

Two hundred fifteen separate procedures were performed coded as infrainguinal bypasses, of which 22 procedures were excluded. One hundred fifty seven individuals had HbA_{1c} measurements of which 106 had sufficient measurements over 5 years to obtain GV. Consort diagram is show in Figure 1.

Demographic data are shown in Table I. Median time until last clinic review or investigation was 262 (107−672) days. Thirty four (32.1%) died during the follow-up period, with no difference between the high (36%) and low (30.9%) GV groups ($P = 0.631$). Median time from closest HbA1c to date of surgery was 62 (12.8−172.3) days.

Glycemic Variability

GV > 9.1% was associated with significantly lower median PP than GV < 9.1%, 198 (97−753.5) vs. 713 (166.5−1,044.5) days ($P = 0.045$) (Fig. 2). However, when assessing GV in only people with DM, there was a nonsignificant trend between the 2 groups median PP GV > 9.1% 198 (105−377) versus GV < 9.1% 489 (195−1,287) days ($P = 0.075$), likely due to small numbers in the cohorts causing type 2 error.

GV was not associated with SP ($P = 0.094$). However, GV was associated with amputation-free survival time when analyzing the whole cohort GV < 9.1, 1,018 (562−1,255) versus GV > 9.1 1,170 (946−1,415) ($P = 0.037$).

Univariate and Multivariate Predictors

Univariate predictors of PP are displayed in Table II. GV > 9.1% versus <9.1% was significantly associated with PP (hazard ratio [HR] 1.85 [CI 1.091−3.136], $P = 0.022$). The only other univariate predictor of PP was bypass level, with below knee bypasses (HR 2.31 [CI 1.164−4.564], $P = 0.017$), and tibial (HR 2.00 [CI 1.022−3.090], $P < 0.043$) having lower PP than above knee bypasses. Smoking status, diabetes status, IHD, nonelective versus elective surgery, and Rutherford stage were not significantly associated with PP in this study.

After multivariate adjustment (Table III), GV remained a significant independent predictor of PP, HR 1.96 (95% CI 1.124−3.417, $P = 0.018$). Above knee versus below knee bypass level also remained an independent predictor of PP, HR 2.54 (95% CI 1.235−5.215, $P = 0.011$).

DISCUSSION

Our study has shown that PP of infrainguinal bypass grafts is significantly impacted by GV, as measured by SD of HbA_{1c}. Individuals with high GV had a significantly shorter PP, with those having a nearly

Table I. Patient demographics

Demographics	HbA_{1c} variability >9.1% ($n = 25$)	HbA_{1c} variability <9.1% ($n = 81$)	*P* value
Age (years)	63.7 (7.5)	72.5 (7.5)	<0.001
Male (%)	19 (76.0)	50 (61.7)	0.191
Female (%)	6 (24.0)	31 (38.3)	
Elective (%)	8 (32.0)	38 (46.1)	0.188
Nonelective admission (%)	17 (68.0)	43 (53.9)	
Rutherford Stage (%)			
3	5 (20.0)	21 (25.9)	
4	3 (12.0)	17 (21.0)	0.421
5	17 (68.0)	43 (53.1)	
Bypass (%)			
AK Pop	7 (28.0)	19 (23.5)	
BK pop	5 (20.0)	32 (39.5)	0.192
Tibial	13 (52.0)	30 (37.0)	
Conduit (%)			
Autologous vein	18 (72.0)	48 (59.3)	
Prosthetic	7 (28.0)	30 (37.0)	0.343
Biological prosthetic	0 (0)	3 (3.7)	
Antiplatelet/Anticoagulants (%)			
Aspirin	3 (12.0)	15 (18.5)	
Clopidogrel	7 (28.0)	27 (33.3)	
Dual antiplatlet therapy	4 (16.0)	8 (9.9)	0.675
Anticoagulants	5 (20.0)	19 (23.5)	
Anticoagulants and antiplatelets	6 (24.0)	12 (14.8)	
Statins (%)	23 (92.0)	73 (90.1)	0.779
Current Smoker	13 (52.0)	26 (32.1)	
Ex-smoker	9 (36.0)	26 (32.1)	0.137
Never Smoker	3 (12.0)	29 (35.8)	
Diabetes	25 (100)	50 (61.7)	<0.001
HTN	12 (48.0)	54 (66.7)	0.92
IHD	10 (40.0)	33 (40.7)	0.947
CBVD	4 (16.0)	13 (16.0)	0.995
COPD	2 (8.0)	15 (18.5)	0.21
Median [IQR] hospital stay (days)	12 [7−27]	7 [5−17]	0.099
Mean Hb (g/L)	112 (25.2)	120 (22.5)	0.164
Creatinine	71 [56−114.5]	82 [67.3−102]	0.567
Median PP (days)	198 [97−753.5]	713 [166.5−1044.5]	0.045
Median SP (days)	747 [168.5−1,099.5]	899 [301−1,216]	0.094
Amputation during follow-up period	8 (32)	9 (11.1)	0.13
Median Amputation-free survival time (days)	1,018 [562−1,255]	1,170 [946−1,415]	0.037
Died during follow-up	9 (36)	25 (30.9)	0.631

PP, primary patency; SP, secondary patency; Hb, hemoglobin; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CBVD, cerebrovascular disease; IHD, ischemic heart disease; HTN, hypertension.

2-fold increased risk of graft thrombosis, even after adjustment. GV on multivariate adjustment was still significant compared to diabetes status alone which was not significant. This suggests that GV might be a more important predictor than diabetes status.

In the current literature, the strength of the association between GV and adverse outcomes is varied.[20] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial found that GV (in HbA_{1c} and fasting blood glucose [FBG]) in patients with longstanding type 2 diabetes was associated with increased risk of macrovascular events, microvascular events, and all-cause deaths, independent of cardiovascular risk factors and mean HbA_{1c} and FBG.[21] Furthermore, a cohort in Rio de Janeiro

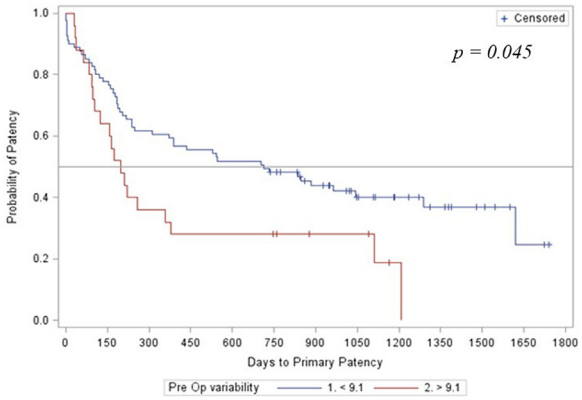

Fig. 2. Kaplan-Meier plot of effects of glycemic variability >9.1% on primary patency.

showed that HbA_{1c} and FBG variability were better risk predictors than mean HbA_{1c} levels for all microvascular and macrovascular complications and all-cause mortality outcomes, excluding retinopathy and peripheral neuropathy.[6] Within surgery, some studies have shown short-term GV, as measured by FBG to be a predictor of major adverse events following coronary artery bypass graft surgery.[22,23] However, some studies have not been able to demonstrate the association.[12,19,24] In a study with 4,982 participants, Echouffo-Tcheugui et al. demonstrated an association between GV and mortality, but found no significant association between GV and cardiovascular disease incidence.[12]

Previous work has shown that GV, as determined by high FBG variability, is associated with increased prevalence of PAD in people with[25,26] and without diabetes.[27,28] Furthermore, high HbA_{1c} variability has been shown to be a risk factor for PAD, in patients with type 2 diabetes.[25,29] However, until now there has been no work assessing if GV is associated with adverse outcomes following PAD intervention.

The mechanism by which GV contributes to the increased risk of cardiovascular disease is attributed to increased oxidative stress and endothelial dysfunction.[15,30–32] Studies have demonstrated that glycemic fluctuations result in a proatherosclerotic state leading to increased inflammatory cytokines, oxidative stress, endothelial dysfunction, and insulin resistance, which is more damaging than sustained hyperglycemia.[28,33,34]

However, associations seen with GV may just be a consequence of poor lifestyle. Fluctuating glycemia is often attributed to with poor glycemic control in general and more specifically, poor adherence to glucose lowering medications and insulin.[18] Furthermore, poor glycemic control could be associated with other unhealthy lifestyle choices which would confound the association of GV and vascular complications. Furthermore, intermittent adherence to diabetes treatment leading to greater GV may be associated with delayed presentation to vascular surgery and clinic nonattendance. Further investigation into the social factors which affect GV and lifestyle choices is needed to evaluate this effect.

There are a number of factors that influence outcomes in lower limb revascularization. Other recognized factors affecting graft patency which we did not report as significant on multivariate adjustment in this study include smoking status, diabetes status, cardiovascular comorbidities, emergency versus elective surgery, and more recently female gender. In a recent study, females had a greater risk of developing periprocedural complications, amputations, and dying.[35] Furthermore, several studies have shown women to have significantly lower graft patency.[36,37] This could therefore be a potential confounder.

However, we did consider several other possible confounders including baseline demographics, preprocedure blood results (renal function and hemoglobin), medications (antiplatelet, anticoagulants, statins), procedure details, length of stay, and comorbidities. Significance was assessed and factors with significance $P < 0.10$ were entered in multivariate analysis, thus increasing the validity of our findings.

There are number of limitations with study, namely the small sample size due to it being a single-center cohort, which reduces validity. HbA_{1c} variability was assessed using the entire cohort and not analyzed on just people with known diabetes, due to a small sample size. However, it is expected that with a larger sample size, similar associations would also be seen in the population with diabetes. Despite the small sample size, our findings are in keeping with similar studies in the area.

Our study may have limited validity due to the lack of access to GP records, therefore we were unable to record the duration of diabetes, diabetes type, and insulin use, and these could have been confounders which we would have adjusted for. Insulin use particularly could have had a confounding effect on vascular complications due to its anti-inflammatory properties[38] which could have been protective against bypass graft failure. It also should be noted that HbA_{1c} might not always be reliable due to the impact of the patient's preoperative Hb. Furthermore, some patients received blood transfusions which would affect the HbA_{1c}. However, this effect would be minimal.

Table II. Univariate predictors of primary patency

Variable	Unadjusted HR	95% CI		Pairwise *P* value	Estimate *P* value
Diabetes Yes versus No	1.589	0.916	2.759	0.0996	
HbA1c SD	1.85	1.091	3.136	0.0224	
2. > 9.1% vs. 1. < 9.1%					
Current Smoker Yes versus No	0.975	0.593	1.602	0.9199	
IHD Yes versus No	1.066	0.661	1.719	0.7932	
Surgery	1.227	0.758	1.985	0.4043	
Nonelective versus Elective					
Rutherford 4 vs. 3	1.901	0.897	4.025	0.0935	0.2445
Rutherford 5 vs. 3	1.382	0.739	2.586	0.3109	
Bypass type BK versus AK	2.305	1.164	4.564	0.0166	0.0505
Bypass type Tibial versus AK	1.999	1.022	3.909	0.0429	

CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; SD, standard deviation.

Table III. Multivariate predictors of primary patency *(HbA1c SD Model)*

Variable	Adjusted HR	95% CI		Pairwise *P* value	Estimate *P* value
HbA1c SD	1.96	1.124	3.417	0.0177	
2. > 9.1% vs. 1. < 9.1%					
Current Smoker Yes versus No	1.117	0.658	1.897	0.6825	
IHD Yes versus No	0.928	0.563	1.528	0.7686	
Surgery	1.105	0.616	1.982	0.7377	
Nonelective versus Elective					
Rutherford 4 vs. 3	1.632	0.722	3.686	0.2391	0.3643
Rutherford 5 vs. 3	1.085	0.487	2.418	0.8419	
Bypass type BK versus AK	2.538	1.235	5.215	0.0112	0.0379
Bypass type Tibial versus AK	2.013	0.97	4.179	0.0605	

HR, hazard ratio; CI, confidence interval; IHD, ischemic heart disease; SD, standard deviation.

It is recognized that there are many ways to measure GV. A systematic review found that 13 indicators were used to measure GV, with SD being the most common.[39] However, it is contested as to which method is the best measure of GV. A paper on the International Consensus on Use of Continuous Glucose Monitoring suggests that coefficient of variation, SD divided by the mean, should be primary measure of GV with SD being a secondary method.[40] We used SD as it is the most commonly used method in previous studies. Furthermore, its simple calculation enables ease of application to the wider clinical setting. However, a drawback of using SD is that it assumes a normal distribution of data but glucose measures are usually not, as noted by Suh and Kim,[41] which could affect the validity of measures.

Previous research has demonstrated the importance of glycemic control in surgery; however, these studies have only included mean FBG and mean HbA_{1c}. Singh et al. showed that poor preoperative glycemic control in patients with DM undergoing infrainguinal lower limb bypass was associated with an increased risk of in-hospital limb events.[42] Moreover, other studies have shown that following PAD revascularization, patients with poor glycemic control were at higher risk of amputation and major adverse limb events.[43,44] Previous studies have also reported that poor perioperative glycemic control is associated with lower patency and higher restenosis rates after lower limb revascularization.[45–47] However, to our knowledge, this is the first study to use GV as a measure of glycemic control to assess PP following infrainguinal bypass.

We have demonstrated that greater GV, as measured by SD of HbA_{1c}, is significantly associated with both lower PP. This suggests that GV might be an important measure of glycemic control and predictor of adverse outcomes in addition to mean HbA_{1c}. This has been explored by others.[20] Gorst et al. also found that HbA_{1c} variability is associated with microvascular and macrovascular complications and mortality independent of the HbA_{1c} level.[8]

Our study is the first to provide evidence of the GV effect on outcomes following infrainguinal bypass suggesting that GV should be an additional

measure of glycemic control. Consistent control that ensures both minimum fluctuation[21] and low mean HbA_{1c} might be the new therapeutic goal for perioperative/postoperative risk reduction. Using SD of HbA_{1c} could have a future role in clinical assessment and could be used for risk stratification preoperatively and postoperatively, particularly for elective interventions. For example, whether surgical patients with greater HbA_{1c} variability should receive more graft surveillance or have stricter glycemic control with greater endocrinology input.

Currently, the best practice perioperative measure of glycemic control is mean HbA_{1c}. People with diabetes undergoing preoperative assessment with an $HbA_{1c} > 69$ mmol/mol should be referred to the diabetes specialist team for glycemic optimization.[3] This study argues that GV should be considered in addition to mean HbA_{1c} in preoperative assessment. Identification during preoperative assessment of patients with greater GV and subsequent referral to diabetes specialists for glycemic optimization could improve graft patency and risk of adverse limb events for elective procedures. However, if primary care were to also identify and refer patients with suboptimum GV early, this could also improve outcomes for emergency operations as well. Further research is needed to investigate the feasibility of using GV for preoperative assessment and surgical management considerations.

CONCLUSIONS

In summary, we have shown that GV, as measured by SD of HbA_{1c}, is a significant predictor of PP following infrainguinal bypass for PAD, even when fully adjusted for confounding. Those with greater GV had a nearly 2-fold increase in risk of graft failure. Therefore, optimizing GV could be an additional therapeutic target to improve postoperative outcomes.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Daniel J. Farndon: Conceptualization, Data curation, Investigation, Methodology, Writing — original draft, Writing — review & editing. **Philip C. Bennett:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing — original draft, Writing — review & editing. **Ian Nunney:** Formal analysis, Methodology, Software, Writing — original draft, Writing — review & editing. **Ketan Dhatariya:** Conceptualization, Methodology, Supervision, Validation, Writing — original draft, Writing — review & editing.

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