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ORIGINAL ARTICLE – OPEN ACCESS

Influence of HbA1c Level on Long-term Coronary Artery Bypass Graft Patency

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ABSTRACT

Objective: Diabetes mellitus (DM) is a very important prognostic factor in patients with coronary artery disease. The precise effects of controlled or uncontrolled diabetes on bypass graft patency in the long term have not yet been determined. The aim of this study was to assess the effect of the glycated hemoglobin (HbA1c) level on bypass graft patency and contribute information about HbA1c targets for patients with diabetes and a history of bypass surgery.

Materials and Methods: A total of 606 patients who underwent coronary bypass surgery and coronary angiography were evaluated. Grafts with any stenosis not causing flow restriction were accepted as patent. The average of all available HbA1c measurements within a year of the angiography was used for analysis. Patients were also analyzed according to the average HbA1c level: well-controlled DM was defined as an average HbA1c level of <7% and uncontrolled DM was defined at an HbA1c level of ≥7%.

Results: In all, 114 patients were included in the study, yielding a total of 289 grafts (venous: 182, arterial: 107). The median HbA1c value of the study population was 7.5 mg/dL. The occlusion rate of arterial and venous grafts was 12.4% and 28.2%, respectively. The median graft age was 8.0 years. The HbA1c level was similar in arterial and saphenous grafts according to the presence or absence of occlusion.

Conclusion: The HbA1c level was not associated with long-term coronary bypass graft patency. Only a graft age of >5 years was significantly associated with long-term venous graft patency. Studies with patients whose HbA1c level is more strictly controlled may reveal different results.

Keywords: Bypass graft patency, coronary artery bypass surgery, diabetes mellitus, glycated hemoglobin, saphenous vein graft

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INTRODUCTION

Diabetes mellitus (DM) is an important prognostic factor among patients with coronary artery disease (CAD). The cardiovascular mortality risk is greater in patients with DM. Patients with DM often develop diffuse and multivessel CAD with involvement of the left main coronary artery and distal small vessels (1). Overall, the current evidence still favors coronary artery bypass grafting (CABG) as the revascularization strategy for patients with diabetes and multivessel disease (2). Surgical procedural factors and graft selection are important factors that determine long-term graft patency. Internal thoracic artery (ITA) grafts to the left anterior descending (LAD) coronary artery appear to have demonstrated the best results (3).

The level of glycated hemoglobin (HbA1c) is used for the diagnosis of DM and monitoring glycemic control (4). An elevated HbA1c level is a risk factor for macrovascular diseases and is associated with increased mortality in patients with CAD (5, 6). The extent of CAD is significantly correlated with the HbA1c level (7). For the majority of patients with diabetes and CAD, a target HbA1c level of <7% is recommended (1). This level is generally related to reduced microvascular complications; there is little evidence available for an HbA1c target to reduce macrovascular risks. HbA1c targets should be individualized according to patient characteristics, particularly age. For elderly patients who may be frail and have multiple comorbidities, a higher target HbA1c level (e.g., <8% or ≤9%) is often suggested to avoid hypoglycemic episodes (8).

It is not yet clear how or if controlled or uncontrolled DM may affect long-term graft patency in patients who undergo a CABG procedure. The objective of this study was to examine the effect of the HbA1c level on long-term bypass graft patency in diabetic patients in both arterial and saphenous vein (SV) grafts. This could provide important information about how strict HbA1c targets should be for patients with diabetes who undergo bypass surgery.

MATERIALS and METHODS

This study was approved by the Karadeniz Technical University Ethics Committee on May 6, 2021 (no: 13).

Table 1. Baseline clinical characteristics of the study groups

	SV grafts			ITA grafts		
	Occluded (n=51)	**Patent (n=63)**	**p**	**Occluded (n=13)**	**Patent (n=94)**	**p**
Age (years)	67.4±9.5	67.0±8.8	0.840[c]	65.2±11.7	67.0±8.3	0.480[c]
Female, n (%)	12 (23.5)	11 (17.5)	0.422[a]	3 (23.1)	18 (19.1)	0.716[b]
HT, n (%)	46 (90.2)	51 (81)	0.168[a]	12 (92.3)	79 (84)	0.686[b]
HPL, n (%)	35 (68.6)	33 (52.4)	0.079[a]	9 (69.2)	57 (60.6)	0.762[b]
Smoking, n (%)	8 (15.7)	6 (9.5)	0.319[a]	1 (7.7)	13 (13.8)	1.000[b]
ACEI/ARB, n (%)	33 (64.7)	30 (47.6)	0.068[a]	10 (76.9)	52 (55.3)	0.23[b]
Beta-blocker, n (%)	42 (82.4)	52 (82.5)	0.979[a]	11 (84.6)	76 (80.9)	1.000[b]
Statin, n (%)	43 (84.3)	46 (73)	0.147[a]	11 (84.6)	72 (76.6)	0.728[b]
ASA, n (%)	47 (92.2)	59 (93.7)	1.000[b]	12 (92.3)	89 (94.7)	0.549[b]
Clopidogrel, n (%)	25 (49)	27 (42.9)	0.511[a]	5 (38.5)	45 (47.9)	0.524[a]
Dual AP, n (%)	22 (43.1)	26 (41.3)	0.841[a]	4 (30.8)	43 (45.7)	0.308[a]
OAD, n (%)	45 (88.2)	56 (88.9)	0.913[a]	11 (84.6)	85 (90.4)	0.621[b]
Insulin, n (%)	9 (17.6)	17 (27)	0.237[a]	3 (23.1)	21 (22.3)	1.000[b]
Graft age, years	8 (6–14)	7 (3–11)	0.110[d]	6 (3–9)	8 (4–12)	0.267[d]
Graft age ≥5 years, n (%)	43 (84.3)	41 (65.1)	**0.020**[a]	9 (69.2)	70 (74.5)	0.739[b]
LVEF (%)	48 (45–55)	50 (45–60)	0.163[d]	45 (45–50)	50 (45–60)	0.124[d]
HbA1c, mg/dL	7.8 (7–9.2)	7.4 (6.4–8.6)	0.063[d]	8.1 (7.3–11.2)	7.5 (6.7–8.8)	0.154[d]
HbA1c ≥7 mg/dL, n (%)	40 (78.4)	40 (63.5)	0.083[a]	11 (84.6)	62 (66)	0.219[b]
Cholesterol, mg/dl	170.9±47.6	178.4±54.5	0.521[c]	184.4±46.0	176.7±53.6	0.699[c]
LDL, mg/dl	103 (80–134)	96 (77–149)	0.903[d]	114.5 (87.5–145.5)	98 (76–140)	0.239[d]
Triglyceride, mg/dl	142 (99–209)	145 (109–193)	0.694[d]	163 (96–227)	145 (108.5–193)	0.861[d]

a: Chi-squared test; b: Fisher's exact test; c: Two-sample t-test; d: Mann-Whitney U test. Frequency (percent); Mean±SD; median (Q1–Q3); ACE: Angiotensin-converting enzyme; AP: Antiplatelet; ARB: Angiotensin receptor blocker; ASA: Acetylsalicylic acid; HbA1c: Glycated hemoglobin; HPL: Hyperlipidemia; HT: Hypertension; ITA: Internal thoracic artery; OAD: Oral antidiabetic; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; SV: Saphenous vein

Diabetic patients were included in this retrospective study if coronary angiography (CAG) results from at least 1 year after CABG and at least 3 HbA1c measurements within a year of the index angiogram were available. Initially, a total of 606 patients with a history of CABG who underwent CAG were evaluated, and among them, 150 were under treatment for DM. Thirty-six were excluded due to insufficient HbA1c level data. The remaining 114 patients, a total of 182 SV and 107 arterial grafts, were included in the study. Only patients with internal thoracic artery (ITA) grafts were included, as there was only a small number of other arterial grafts. All of the CAG results were evaluated and the grafts were classified as patent or occluded. Any stenosis not causing flow restriction was considered a successful endpoint for a bypass graft; no classification according to degree of stenosis was used. Any hemodynamically significant stenosis is treatable, and treated grafts will remain patent for a period of time. Therefore, we classified the grafts as patent regardless of the stenosis degree and as occluded when there was no distal flow. Patients with acute coronary syndrome were excluded from the study. Demographic data, including details of age, gender, coronary risk factors, and ongoing medication use, were obtained from the medical database. The average of all available HbA1c measurements within 1 year was used for analysis. As specified in the 2019 European Society of Cardiology Guidelines for diabetes, pre-diabetes, and cardiovascular disease, a 7% mg/dL HBA1c cut-off value was used to group patients as controlled or uncontrolled DM. Two types of analysis were performed: First, the patients were grouped and analyzed according to the presence or absence of occlusion in ≥1 graft; second, all of the grafts were evaluated individually as occluded or patent.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 software (IBM Corp., Armonk, NY, USA). Normal distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Chi-squared and the Fisher's exact tests were used to compare categorical variables according to group. Normally distributed data and non-normally distributed data were compared using a 2-sample (independent) t-test and the Mann-Whitney U test, respectively. Continuous variables were expressed as the mean+SD or median (Q1–Q3), whereas categorical variables were expressed as frequencies and percentages. Univariate and multiple logistics regression analysis (enter model) were used to examine the risk factors (graft age and HbA1c) affecting SV graft patency. The multiple logistics regression model demonstrated goodness-of fit (χ^2=8.415; p=0.015). HbA1c cut-off points were generated to calculate the sensitivity and specificity of graft

Table 2. Glycated hemoglobin level in different graft types

	SV-CX		SV-RCA		SV-DIA		ITA	
	Patent	Occluded	Patent	Occluded	Patent	Occluded	Patent	Occluded
HbA1c (mg/dL)	8 (7.2–9.5)	7.4 (7–7.9)	7.3 (6.8–9)	8.1 (6.9–9.2)	8 (7–8.4)	9.4 (7.9–10.9)	7.5 (6.7–8.8)	8.1 (7.3–11.2)
P value*	0.137		0.389		0.443		0.154	

*: Mann-Whitney U test; Median (Q1–Q3); HbA1c: Glycated hemoglobin; ITA: Internal thoracic artery; SV-CX: Saphenous vein to the circumflex coronary artery; SV-DIA: Saphenous vein to the diagonal coronary artery; SV-RCA: Saphenous vein to the right coronary artery

Table 3. Univariate and multiple logistics regression analysis of patency of SV grafts

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
SV graft age ≥5 years	2.884 (1.155–7.203)	**0.023**	2.861 (1.134–7.218)	**0.026**
HbA1c ≥7 mg/dL	2.091 (0.901–4.851)	0.086	2.069 (0.876–4.89)	0.097

CI: Confidence interval; HbA1c: Glycated hemoglobin; OR: Odds ratio; SV: Saphenous vein

Table 4. Saphenous vein graft patency rate according to glycated hemoglobin group

	Median patency (95% CI)	p
HbA1c (mg/dL)		0.058
<7	16 (13.071–18.929)	
≥7	14 (9.826–18.174)	

*: Log-rank test; CI: Confidence interval; HbA1c: Glycated hemoglobin

occlusion using receiver operating characteristic (ROC) curves. Graft age was used as survival time and a log-rank test was used to compare graft survival according to HbA1c groups. The significance level applied was p<0.050.

RESULTS

A total of 114 patients (182 SV and 107 arterial grafts) were included in the study. The mean age of the study population was 67±9 years, and 80% (n=91) of the patients were male. Hypertension was present in 68.1% (n=77) of the patients, and 9.7% (n=11) were smokers. In all, 74.3% (n=84), 36.8% (n=42), and 34.0% (n=38), received antiaggregant treatment with acetylsalicylic acid, clopidogrel, or both, respectively. The treatment used for DM was oral medication in 70.8% (n=80) and insulin in 18% (n=20). The average HbA1c level of the study population ranged from 5.4 to 12.9 mg/dL (median: 7.5 mg/dL). The median graft age was 8.0 years (range: 4–12 years). The occlusion rate of arterial grafts and SV grafts was 12.4% (n=13) and 28.2% (n=51), respectively (Table 1). Although the HbA1c levels were slightly higher in the occluded group for both arterial and SV grafts, the difference was not statistically significant. (P values: 0.389, 0.137, 0.443, 0.154 for SV right coronary artery, SV circumflex artery, SV diagonal, and ITA grafts, respectively) (Table 2). The ROC curve analysis revealed no statistically significant HbA1c cut-off value for graft occlusion. When the possible factors were identified with univariate and multiple logistics regression analysis, only a graft age of ≥5 years was found to be significant in the occluded group of SV grafts (odds ratio: 2.861 [95% confidence interval: 1.134–7.218]; p=0.026) (Table 3). Kaplan-Meier analysis depicting graft age-related events and the relationship between controlled and uncontrolled diabetes grouped by HbA1c level did not reveal a significant difference between groups (p=0.058) (Table 4) (Fig. 1).

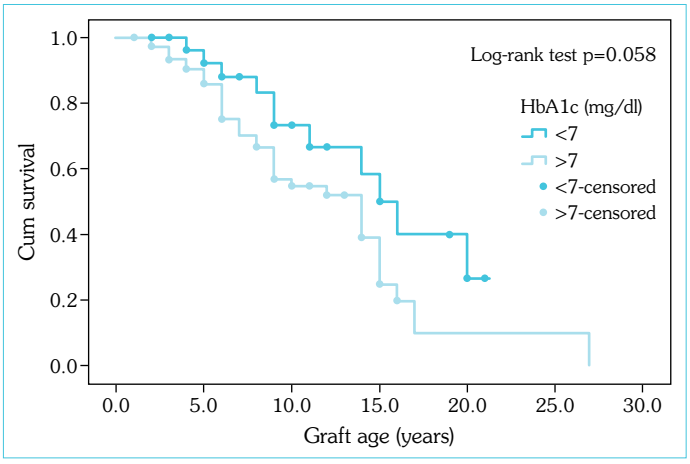

Figure 1. Kaplan-Meier curves depicting graft age-related events and the relationship between controlled and uncontrolled diabetes grouped by glycated hemoglobin (HbA1c) level

DISCUSSION

No significant relationship was observed between long-term graft patency and HbA1c level in either ITA or SV grafts. This result contradicted the hypothesis that poor diabetic control would have a negative effect on bypass graft patency. However, the relationship between graft patency and graft age was found to be significant, which is consistent with the literature. Similarly, in the long term, ITA graft patency was better than that of SV grafts.

Since cardiac mortality after a bypass was observed to be similar in diabetic and non-diabetic patients in the BARI2 study, many other studies have been conducted to further investigate the effect of diabetes on bypass graft patency. While some of the research has suggested a relationship between diabetes and graft patency, other work has failed to find a relationship (9). In the most recent large study, no significant difference was seen in long-term graft patency between diabetic and non-diabetic patients (3). The graft patency rates were similar to our results in ITA grafts (87.6% vs. 85%), whereas SV graft patency was poorer (74.8% vs. 67%). This may be related to the 20-year follow-up duration of the study.

In the early period after bypass, graft occlusion is most often a result of factors related to the procedure, such as thrombosis, inflammation, endothelial dysfunction, or intimal hyperplasia (10). In the long term (>5 years), occlusion develops with atherosclerotic plaque formation due to lipid accumulation and lumen narrowing due to neointimal hyperplasia. Only some 50% to 60% of grafts remain open after 5 years. However, 90% of arterial grafts remain patent at 10 years. Many studies have evaluated the factors affecting graft patency. The most important of these factors are the age and the type of graft used, the characteristics of the native coronary artery where the graft is anastomosed, and the degree of stenosis (11, 12). Factors such as patient age, triglyceride levels, smoking habit, and increased inflammation have also been shown to be associated with graft patency (13–15). Inflammation parameters and the severity of stenosis of the anastomotic vessel were not evaluated in our study. The use of medications like an antiaggregant, beta-blocker, or statin, which may affect graft patency, were also similar between the groups (16).

Graft age is the most important factor for SV graft patency. In our study, the average graft age was 8.5 years, which is longer than previous studies in the literature. In many studies, the SV graft occlusion rate in diabetic patients was found to be around 25% in 5 years. Therefore, the effect of diabetes and especially HbA1c on graft patency may not be accurately demonstrated. Evaluation of HbA1c levels in short-term studies may yield different results. Although the mean age of the grafts was 8.5 years, the average of the last year was used in the evaluation of HbA1c. This may also have affected the results.

HbA1c level has been used to determine long-term blood glucose control and has been demonstrated to affect clinical outcomes. HbA1c can cause damage via inflammation and other complex mechanisms and result in atherosclerotic plaque formation on vessels. It has been established that an elevated HbA1c level is a risk factor for macrovascular diseases and indicates an increased risk of CAD mortality. Studies investigating the effect of HbA1c levels on clinical outcomes after CABG surgery have revealed conflicting results. Many studies have investigated early complications, such as postoperative infection, mortality, and cerebral diseases, and a few have evaluated long-term mortality (4, 17). In a systematic review, high HbA1c levels were found to be correlated with poor outcomes (17). However, the relationship of these poor results with the graft occlusion could not be clearly identified. Poor outcomes were mostly attributed to causes such as progression of native vascular disease, heart failure, hypertension, renal insufficiency, and peripheral artery disease, which are very common in diabetic patients. The difference in mortality between the groups was not evaluated in our study, but poor diabetic control did not affect the graft patency in the long term. Therefore, it could be speculated that poorer clinical outcomes may not simply be related to graft patency in uncontrolled DM patients. It has been shown that intensive glycemic control may not protect diabetic patients with multiple comorbidities from cardiovascular adverse events (18).

To prevent macrovascular disease, it seems reasonable to maintain the HbA1c level <7%, as recommended in some guidelines (1). In selected patients with a low risk of hypoglycemia and no significant cardiovascular disease, targets may be reduced to prevent microvascular complications, however, the potential risks of intensive glycemic control may outweigh the benefits in patients with a history of severe hypoglycemia and severe frailty. Less stringent HbA1c targets (7.5–8.0%) may be safer in these patients (19).

The most important limitation of the study is its retrospective design. In addition, since the average graft age was 8.5 years, the HbA1c effect could not be fully evaluated, considering that most SV grafts are occluded after 5 years. The high mean HbA1c level did not reflect the results seen in better-controlled patients. The evaluation of HbA1c levels from only within the previous year is another limitation. In addition, it is also important to note that other factors that could affect graft patency, like graft and procedure-related factors and inflammation, were not evaluated. Due to confounders with multiple grafts, some patent and some occluded, the effect of HbA1c was measured separately for all grafts.

CONCLUSION

This study aimed to reveal the effect of glycemic control on bypass graft patency in diabetic patients. The results indicated that graft patency was similar in diabetic patients regardless of HbA1c level, which supports the findings of some previous studies. Hence, strict diabetic control would not appear to improve or preserve graft patency in long term. Prospective studies with a larger number of patients are needed to further explore and confirm these results.

Ethics Committee Approval: The Karadeniz Technical University Clinical Research Ethics Committee granted approval for this study (date: 06.05.2021, number: 13).

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Author Contributions: Concept – MŞ; Design – MŞ, SÖ; Supervision – OET, MK; Resource – YH, SÖ; Materials – SÖ, OET; Data Collection and/or Processing – SÖ, MŞ; Analysis and/or Interpretation – SÖ, OET; Literature Search – YK, MŞ; Writing – MŞ, MK; Critical Reviews – MK, MŞ.

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