The Relationship Between Glycosylated Hemoglobin and Myocardial Perfusion Imaging

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ABSTRACT

Background: The relationship between long-term glucose control (measured by glycosylated hemoglobin [HgbA1C]) and myocardial perfusion imaging (MPI) abnormalities in symptomatic diabetic patients has not been studied.

Hypothesis: We hypothesized that diabetic patients with poorly controlled HgbA1C would have more abnormal MPI compared to both patients without diabetes and diabetic patients with tighter glycemic control.

Methods: This was a retrospective evaluation of 1037 consecutive patients referred for MPI. All patients completed a 1-day MPI protocol. The electronic medical records were accessed for demographics and relevant medical history.

Results: Diabetic patients had a higher risk of abnormal MPI (including ischemia, infarction, and mixed ischemia/infarction) compared to nondiabetic patients (relative risk [RR] = 1.77). The populations with suboptimal (HgbA1C $\geq 7\%$) and poor (HgbA1C $\geq 8\%$) glycemic control had significantly higher risk of abnormal MPI (RR = 1.78 and 2.17, respectively) compared to nondiabetic patients. Coronary angiography supported the MPI results; 66% of diabetic patients had coronary artery disease (CAD), which was higher than the 53% of patients without diabetes found to have CAD.

Conclusions: The importance of strict glycemic control to reduce cardiovascular complications in diabetic patients is well known. Our study shows a significantly higher risk of abnormal MPI and CAD in diabetic patients with suboptimal and poor long-term glycemic control, further emphasizing the need for aggressive risk factor modification to minimize vascular complications from DM.

Introduction

Diabetes mellitus (DM), established as a coronary artery disease (CAD) risk factor equivalent, is highly prevalent in the United States.¹ Additionally, cardiovascular disease is the leading cause of death in diabetic patients.² Attributing to this is the fact that more extensive CAD is found in patients with DM as well as the near ubiquitous presence of additional cardiovascular risk factors among the insulin resistant.³

Along with coronary angiography, functional studies such as myocardial perfusion imaging (MPI) are vital to the diagnosis and risk stratification of CAD. Research demonstrating the value of functional studies for diagnosis and prognosis of CAD in the diabetic patient population has been limited. Previous studies have shown that the diagnostic accuracy of exercise tolerance testing alone in patients with DM is low, and studies evaluating the accuracy of stress echocardiography for detecting CAD in diabetic patients have been few in

number and small in sample size.⁴ MPI in such a subpopulation has been more extensively investigated, albeit limitedly.

Demonstrating that the accuracy of MPI for detection of significant obstructive CAD is no different between diabetic and nondiabetic patient populations was pivotal for establishing the groundwork for further investigations.⁵ Studies have suggested that the severity of MPI abnormalities in diabetics is a major contributor to future cardiac death and myocardial infarction.^{6,7} Further work in this field has demonstrated an increased risk of adverse MPI outcomes in men and women with insulin-dependent diabetes compared to those with non-insulin dependent diabetes.⁸ Normal MPI results in patients with DM have been associated with a low cardiac event rate and a 2-year survival rate similar to patients without DM. For these patients, however, cardiac event rates increased after 2 years.⁷ Studies have evaluated the asymptomatic patient as well, finding a higher prevalence of abnormal and high-risk scans. The DIAD (Detection of Ischemia in Asymptomatic Diabetics) study demonstrated that 1 of 5 asymptomatic diabetic patients were found to have silent ischemia, with 1 in 16 having a markedly abnormal MPI.^{9,10}

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Risk factor modification, including glycemic control, is essential to the prevention and management of CAD. Few prior studies have evaluated the relationship of long-term glucose control in patients with DM, measured by glycosylated hemoglobin (HgbA1C), relative to the burden of CAD.^{11,12} DeLuca et al noted the prevalence silent myocardial ischemia detected by MPI was greater in patients with poorly controlled diabetes (HgbA1C $\geq 7.6\%$) compared to patients with better control (HgbA1C $< 7.6\%$).¹¹ In a symptomatic diabetic population, increasingly severe CAD noted by angiography correlated with increasing HgbA1C levels.¹² Our study differs from these studies in that we hypothesized that symptomatic diabetic patients with poorly controlled HgbA1C would have more abnormal MPI compared to both nondiabetic patients and diabetic patients with tighter glycemic control.

Methods

The study was approved by the institutional review boards at Saint Vincent Hospital and Fallon Clinic, both in Worcester, Massachusetts.

Patient Selection

This was a retrospective evaluation of 1037 consecutive outpatients over 6 months referred to a single center for clinically indicated stress testing with myocardial perfusion imaging. The electronic medical records were used for access to patient demographics and relevant medical history including prior CAD and risk factor profile. For this study, diabetic patients (either type 1 or 2) were defined as individuals taking a hypoglycemic agent (either an oral agent or insulin) or patients with HgbA1C value in the past 12 months $\geq 6\%$.

Myocardial Perfusion Imaging Protocol

All patients completed either a symptom-limited exercise test using a standard Bruce protocol or received a weight-based Persantine (Baxter Healthcare Corporation, Deerfield, IL) infusion over 4 minutes followed by 4 minutes of low-level treadmill exercise if able to exercise. A 1-day imaging protocol was performed using approximately 10 mCi of technetium 99m-sestamibi for rest imaging and approximately 30 mCi of technetium 99m-sestamibi injected at peak stress for stress imaging. Single photon emission computed tomography (SPECT) imaging was performed using a Siemens AG (Munich, Germany) Orbiter camera with a 9th-order Butterworth filter. Gated acquisition was performed on the stress images. Images were analyzed with Mirage (Segami, Columbia, MD) software without the use of motion correction or attenuation correction software. All studies were interpreted in the usual course of practice by cardiologists with Certification Board of Nuclear Cardiology certifications who had no knowledge of the HgbA1C levels. The study was considered abnormal if ischemia, infarct, or a combination of ischemia and infarct was present.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5.02 (GraphPad Software, Inc., La Jolla, CA) statistical

software program. Unpaired *t* test was used to analyze the difference between the diabetic and nondiabetic groups. Significance of our results was evaluated using Pearson χ^2 test. A *P* value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 shows the risk factors for CAD in the diabetic and nondiabetic patient populations, indications for MPI, and the type of stress test performed. The diabetic and the nondiabetic patients were clinically similar in gender, tobacco history, total cholesterol values, and indications for stress test. The 2 groups differed in cardiovascular risk factors—patients with DM were older with more hypertension and hyperlipidemia. Diabetic patients were also more likely to be on lipid-lowering agents, more commonly had prior CAD, and underwent more pharmacologic MPIs.

Glycemic Control, MPI, and CAD

As demonstrated in the Figure 1 and Table 2, diabetic patients in this study ($n = 328$, 31.6%) had a higher risk of abnormal MPI (including ischemia, infarction, and mixed ischemia/infarction) compared to patients without DM (odds ratio [OR]: 1.77, 95% confidence interval [CI]: 1.34–2.33, $P < 0.0001$). Well-controlled diabetic patients, HgbA1C $< 7\%$ ($n = 197$), had more abnormal MPI when compared to patients without DM (OR: 1.73, 95% CI: 1.25–2.4, $P = 0.0013$). Seventy-five diabetic patients (22.9% of the DM population) had suboptimal long-term diabetes control, manifest by HgbA1C of $\geq 7\%$ and $< 8\%$. In these patients, abnormal MPI was more likely compared to patients without DM (OR: 1.78, 95% CI: 1.09–2.9, $P = 0.0235$). Fifty-two diabetic patients (15.8%) had HgbA1C of 8% or higher and were considered the poor glycemic control group. The poor glycemic control group had significantly more abnormal MPI (OR: 2.17, 95% CI: 1.23–3.83, $P = 0.0109$) compared to nondiabetics.

Patients were referred for coronary angiography at the discretion of the treating physician. As such, only 18% of all patients had angiographic results available for review and correlation. In both the diabetic and nondiabetic groups, 47% of patients with abnormal MPI subsequently underwent coronary angiography. The presence of obstructive CAD (defined at coronary angiography as a 70% or greater stenosis in 1 or more coronary arteries) supports the MPI results. Of the diabetic patients who underwent coronary angiography, 66% were documented to have obstructive CAD, higher than the 53% rate of angiographically proven obstructive CAD in nondiabetic patients (OR: 1.76, 95% CI: 0.96–3.23).

Discussion

The importance of strict glycemic control in reducing vascular complications from DM is well known.¹³ Patients with diabetes typically have a larger burden of cardiovascular risk factors when compared to nondiabetic patients. Our baseline patient characteristics are consistent with that observation—more diabetic patients had hypertension, hyperlipidemia, and a history of CAD. Our results show

Table 1. Baseline Clinical Characteristics

	DM (n = 328)	Non-DM (n = 709)	P Value
Male	192 (59)	378 (53)	0.12
Age, y	67 ± 12	63 ± 13	<0.0001
Clinical history			
Hypertension	286 (87)	447 (63)	<0.0001
Current smoker	58 (18)	147 (21)	0.28
Hyperlipidemia	292 (89)	472 (67)	<0.0001
Coronary artery disease			
Previous history of CAD	103 (31)	111 (16)	<0.0001
CABG	37 (36)	31 (28)	<0.0001
PCI/angioplasty	53 (51)	58 (52)	0.0002
Myocardial infarction	10 (10)	11 (10)	0.1523
Angiographic evidence	3 (3)	11 (10)	0.5668
Ejection fraction, %	56 ± 12	59 ± 11	<0.0001
Body mass index, kg/m ²	31 ± 5	29 ± 6	<0.0001
Blood pressure, mm Hg			
Systolic	131 ± 18	127 ± 18	0.0009
Diastolic	77 ± 9	78 ± 8	0.0725
Serum lipid levels, mg/dL			
Total cholesterol	165 ± 49	180 ± 48	<0.0001
HDL cholesterol	45 ± 26	50 ± 16	0.0002
LDL cholesterol	91 ± 35	106 ± 33	<0.0001
Medication			
Lipid agent	255 (78)	377 (53)	<0.0001
Hypoglycemic agent	193 (59)	N/A	
Insulin	41 (21)	N/A	
Oral agent	125 (65)	N/A	
Insulin and oral agent	27 (14)	N/A	
Hgb A1C, %	7	N/A	
Exercise MPI	75 (23)	328 (46)	<0.0001
Indication			
Chest pain	174 (53)	374 (53)	0.9467
Dyspnea	53 (16)	100 (14)	0.3975

Table 1. Continued

	DM (n = 328)	Non-DM (n = 709)	P Value
Preoperative	51 (16)	78 (11)	0.0431
Abnormal ETT	10 (3)	48 (7)	0.0136
Abnormal ECG	11 (3)	32 (5)	0.5029
Other	299 (9)	77 (11)	<0.0001

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; ETT, exercise tolerance test; HDL, high-density lipoprotein; HgbA1C, glycosylated hemoglobin; LDL, low-density lipoprotein; MPI, myocardial perfusion imaging; N/A, not applicable; PCI, percutaneous coronary intervention. Other includes abnormal echocardiogram, arrhythmia, history of CAD, congestive heart failure, nonspecific symptoms (dizziness, nausea, fatigue), palpitations, patient request, screening, and syncope. *P* = analysis of variance. Values are mean ± standard deviation or number of patients (percentage).

Figure 1. Diabetic subgroups with increased risk of abnormal MPI when compared to nondiabetics. Abbreviations: DM, diabetes mellitus; HgbA1C, glycosylated hemoglobin.

a higher risk of abnormal MPI in diabetic patients with poor long-term glycemic control compared to both patients without DM and diabetic patients with tighter glycemic control.

Our results are consistent with the results of others demonstrating that CAD risk factor modification reduces MPI abnormalities. Multiple studies have demonstrated that CAD risk factor reduction through intensive medical management reduces MPI abnormalities.^{14–16} Cholesterol is among modifiable risk factors, and it has been shown that administration of pravastatin in patients with CAD and average cholesterol levels improved myocardial perfusion during dipyridamole stress SPECT.¹⁴ The 3-year follow-up to the DIAD study demonstrated resolution of ischemia in 79% of patients with perfusion abnormalities on initial MPI following intensification of treatment with cardiac medications.¹⁵ Additionally, the INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation) trial randomized clinically stable, high-risk patients after acute myocardial infarction to intensive medical therapy vs coronary revascularization. Using serial adenosine SPECT imaging, intensive medical therapy was found to suppress ischemia to a degree comparable to that achieved with revascularization, with

Table 2. Abnormal MPI and Glycemic Control

	No DM [n = 709]	DM [n = 328]	HgbA1C < 7% [n = 197]	HgbA1C ≥ 7% [n = 75]	HgbA1C ≥ 8% [n = 52]
Abnormal MPI	201 (28)	135 (41)	80 (41)	31 (41)	24 (46)
Infarction	38 (19)	27 (20)	16 (20)	4 (13)	7 (29)
Ischemia	118 (59)	64 (47)	40 (50)	15 (48)	9 (38)
Mixed ischemia/infarction	45 (22)	44 (33)	24 (30)	12 (39)	8 (33)

Abbreviations: DM, diabetes mellitus; HgbA1C, glycosylated hemoglobin; MPI, myocardial perfusion imaging. Values are number of patients (percentage).

1-year cardiac event rates comparable between strategies.¹⁶ Of note, the risk factor intensification in the aforementioned studies did not include glycemic control in the analysis. As previously mentioned, DeLuca et al observed an association with glycemic control and abnormal MPI in silent myocardial ischemia, and Ravipati et al described the association of glycemic control with findings on coronary angiography.^{11,12} Our study supports the findings of these previous studies and provides further evidence regarding the importance of long-term glycemic control in symptomatic diabetic patients as a means to reduce abnormal MPI, and thereby presumably reduce CAD and its associated complications.

The retrospective study design is 1 limitation to our study. With that limitation, the potential bias must be highlighted that not all of the patients had a cardiac catheterization; only 18% of all participants and 23% of diabetic patients, at the discretion of their treating physician, underwent cardiac catheterization. Fewer diabetic patients completed an exercise MPI protocol, suggesting a population with poorer exercise tolerance and potentially more underlying CAD. Data were not adjusted for matched variables, creating a potential source for nullification of significance. Additionally, the study is limited by a referral bias, as the majority of patients were referred for testing because of symptoms.

Our diabetic patient population may be overrepresented as those with HgbA1C ~6% may be prediabetics. However, a recent study by Selvin and colleagues suggested that glycated hemoglobin values >6% may be a clinically useful marker to identify persons at risk not only for diabetes but also cardiovascular disease.¹⁷

Conclusion

Our results indicate an increased risk for abnormal myocardial perfusion imaging, and therefore CAD, in diabetic patients, particularly those with suboptimal or poor long-term glycemic control as measured by HgbA1c. These results emphasize the need for aggressive risk factor modification to minimize cardiovascular complications from DM. This also raises the question as to whether asymptomatic patients with poorly controlled DM should undergo a screening stress test with MPI, given the association between poor glycemic control and greater risk of abnormal MPI, as well as underlying CAD seen in this symptomatic population. This would need to be evaluated in future studies of asymptomatic patients with DM. Further investigation would be warranted to prospectively assess

the effect of aggressive glycemic control and the potential for regression of CAD or improvement of MPI results.

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