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Glycosylated Hemoglobin for Diagnosis of Prediabetes in Acute Ischemic Stroke Patients

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Abstract

Background—Prediabetes (PD) is an independent risk factor for stroke. The American Diabetes Association (ADA) has recently published new guidelines recommending glycosylated hemoglobin A1c (HbA1c) as a marker to diagnose diabetes and PD. Diagnosis of diabetes Mellitus (DM) is often made at the time of hospitalization for stroke. Less is known about identifying PD in acute ischemic stroke (AIS) patients. We aim to investigate the frequency of new-onset PD in the hospitalized AIS patients using the new ADA guidelines.

Methods—We retrospectively studied 362 AIS patients from our local database. Stroke risk factors, type of stroke, and white matter hyperintensities (WMHs) were all collected. Based on the 2010 ADA guidelines, patients were classified as prediabetics, with HbA1c levels of 5.7%–6.4%; diabetics, with HbA1c levels more than 6.5%; and normoglycemic, HbA1c levels less than 5.7%. We used SAS 9.3 for analysis.

Results—On admission, 279 (78%) AIS patients had HbA1c values collected. Stratifying by HbA1c, 113 (31%) AIS patients were given the diagnosis of DM and 109 (30%) were given the diagnosis of PD. From the 166 patients with no DM history, 53% had PD and 15% had DM. Patients with DM and PD were more likely to have hypertension ($P < .001$) and hyperlipidemia ($P = .05$). The likelihood of new-onset PD increased with age ($P < .01$). No differences were found by the type of stroke or WMH.

Conclusion—Diabetes and PD are highly prevalent in the hospitalized ischemic stroke (IS) patients. Our results suggest a need for routine HbA1c testing in all patients with IS. Further larger studies need to confirm these findings.

Keywords

Acute ischemic stroke; diabetes; prediabetes; hospitalization

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Introduction

Diabetes Mellitus (DM) is a well-established major risk factor for ischemic stroke (IS).¹ In patients with stroke, diabetes is associated with increased mortality, morbidity, and stroke recurrence.²

Commonly, patients with acute ischemic stroke (AIS) are found to be diabetic after their initial studies during hospitalization. Indeed, the prevalence of undiagnosed diabetes in acute stroke patients is estimated to be between 6% and 42%.^{3–5} As a result, these newly diagnosed DM patients get benefit of early treatment, diabetes education, and appropriate referral to diabetes care. However, less is known about identification, treatment, and management of prediabetes (PD) in acute stroke patients. PD can be defined by impaired glucose tolerance test (IGT) or impaired fasting glucose level.⁶ In 2010, the American Diabetes Association (ADA) published new guidelines that included the use of percent of glycosylated hemoglobin A1c (HbA1c) for the diagnosis of PD.⁶ Recent studies have shown that PD, defined by HbA1c levels, also constitutes an independent risk factor for cardiovascular disease and stroke.^{7,8} Other studies using different criteria for the identification of PD have resulted in conflicting associations between PD and risk of stroke.⁹ In this study, we aimed to investigate the frequency of new-onset PD in AIS patients using HbA1c according to the new ADA guidelines.

Methods

We used our local acute stroke database to identify 362 AIS patients admitted to our University Hospital between January 2008 and December 2009. Baseline National Institutes of Health Stroke Scale and stroke subtypes were extracted from clinical charts. For the retrospective classification of IS subtypes, we used the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study.¹⁰ The allocation of the TOAST classification was based on a computerized algorithm.¹¹ In patients with available magnetic resonance imaging, we studied white matter hyperintensities (WMHs) using the Fazekas rating scale.¹² Based on the 2010 ADA guidelines, all AIS patients with HbA1c levels within the range of 5.7%–6.4% were classified as prediabetics, patients with HbA1c levels more than 6.4% were classified as diabetics, and patients with HbA1c levels less than 5.7% were classified as normoglycemic (NG).⁶ We used SAS 9.3 for data analysis. Differences in mean values of groups were tested for significance by 1-way analysis of variance followed by the Tukey studentized range tests. Differences in proportions were tested by chi-square tests. A *P* value less than .05 denoted statistical significance. Our local Institutional Review Board approved the study.

Results

During hospitalization, 279 (78%) IS patients had HbA1c values collected. From this group, 34% of the patients carried a diagnosis of diabetes type 2. Stratifying by HbA1c, 113 (31%) AIS patients were given the diagnosis of DM and 109 (30%) were given the diagnosis of PD. From the 166 AIS patients with no history of DM, we identified 88 (53%) patients as prediabetics and 25 (15%) as newly diagnosed diabetics. There were 133 AIS patients with a history of DM, 78% of them had HbA1c levels more than 6.4, 18.5% had their HbA1c levels in the PD range, and 3.5% were NG (Fig 1). Patients with DM and PD were more likely to have hypertension (*P* < .001) and hyperlipidemia (*P* = .05) than NG patients. The likelihood of new-onset PD increased with age (*P* < .01). No differences were found by gender, initial National Institutes of Health Stroke Scale, TOAST classification, WMH, or outcomes among the 3 groups (Table 1).

Discussion

Recent epidemiologic study has found a prevalence of 12% of DM and 29% of PD in the US general adult population. The same study accounted for 5% of diabetics who were unaware of their hyperglycemic disorder.¹³ We applied the new ADA guidelines on HbA1c to classify our patients in 3 different glycemic categories. In patients with no history of DM, 15% were categorized as diabetics and 53% as pre-diabetics. Our results concur with other studies that used the 2-hour 75-g oral glucose tolerance test (OGTT) for the detection of IGT in stroke patients.¹⁴ The OGTT is an accurate measure of IGT, and it is considered a better predictor of cardiovascular diseases and conversion to DM. However, its use in AIS patients is limited by the effect of acute illness on the glycemic state and the presence of dysphagia, which is common on the first day after stroke. Another method to diagnose PD is the impaired fasting glucose. The interpretation of fasting glucose to detect diabetes or PD is also hindered by the acute illness. In contrast, the HbA1c level reflects long-term glycemic control and constitutes a more accurate and stable measure than fasting blood glucose levels. HbA1c is widely used in clinical practice to assess control of DM, and in principle, it should not be affected by the acute stroke illness.¹⁵ Despite its simplicity, the clinical use of HbA1c is not widespread in the care of acute stroke patients. Primary stroke center guidelines do not include screening of hyperglycemic disorders with HbA1c. A recent survey on quality of care and outcomes indicated that less than 50% of patients with DM hospitalized with IS are tested with HbA1c.¹⁶

It is known that the prevalence of cardiovascular risk factors such as cholesterol levels and elevated systolic blood pressure increase linearly according to the OGTT.¹⁷ Our results also showed an association between abnormal HbA1c, HTN, and hyperlipidemia. Atrial fibrillation was not associated with elevated HbA1c. The mean age of patients with diabetes and PD was higher than NG, which concurs with the established epidemiologic data that show that the probability of DM and PD increases with aging. These findings support the use of HbA1c for DM and PD screening in stroke patients and the validity of our results.

Some studies have linked HbA1c with small-vessel disease, but we did not find association between the type of stroke and HbA1c. Large cross-sectional studies have found increase of WMHs in diabetics compared with normal controls. WMHs on brain magnetic resonance imaging are a surrogate of cerebral small-vessel disease. We used the Fazekas rating scale score to assess WMHs in our patients, but we found a nonstatistical difference between the groups. This could be explained by the limitation of the Fazekas rating scale for more subtle WMH changes and the small sample size.

It has been noted that prediabetics with HbA1c levels of 6–6.4 are at higher risk to convert into DM. However, obesity and cardiovascular risk factors also increase this conversion rate. Hence, patients with IS might be already at higher risk of developing diabetes or to have an abnormal IGT. Although the conversion rate of a stroke patient with PD into DM is not known, we suggest that patients with HbA1c levels between 5.7 and 6.4 should be followed with OGTT or a new HbA1c level 3 months after their stroke.

Lifestyle modification and pharmacologic therapies with thiazolidinediones or biguanides have demonstrated a reduction of conversion from PD to DM.^{18–20} However, the use of thiazolidinediones or biguanides for secondary stroke prevention in patients with PD is still an unanswered question. The Insulin Resistance Intervention after Stroke trial is a current ongoing trial testing the use of pioglitazone as a secondary stroke prevention.

Our study has limitations for generalization of its findings because of its retrospective design, small sample size, and selected population from our single center. However, our

study highlights the importance of the use of HbA1c as part of stroke workup for identification of diabetes and PD.

Conclusion

PD and diabetes are commonly found in AIS patients. Our results indicate a need for routine HbA1c testing in all patients admitted with AIS. Further studies are needed to confirm our findings in larger populations.

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Figure 1.

Glycosylated hemoglobin (HbA1c) in acute stroke patients. Patients with a known history of diabetes (DM+) and patients with no history of diabetes (DM-). Abbreviation: HbA1c, hemoglobin A1c.

Table 1

Characteristics of acute stroke patients divided by HbA1c

	NG, n = 57	PD, n = 109	DM, n = 113	P
Age (mean $\pm$ SD)	57.1 $\pm$ 16.1	64.9 $\pm$ 15.3	62.1 $\pm$ 13.5	.007
Women (%)	47.4	55.1	54.9	ns
Hypertension (%)	43.8	65.1	79.4	<.0001
Hyperlipidemia (%)	31.6	30.3	45.1	.048
History of DM (%)	3.5	18.6	77.9	<.0001
Atrial fibrillation (%)	8.9	14.6	16.8	ns
NIHSS score, median (IQR)	5 (3–13)	6 (2–11)	4 (2–12)	ns
Ethnicity, n (%)				ns
White	26 (25.0)	43 (41.4)	35 (33.6)	
Hispanic	14 (14.1)	37 (37.4)	48 (48.5)	
Asian	1 (7.7)	4 (30.8)	8 (61.5)	
African-American	0	2 (40)	3 (60)	
Other	16 (27.6)	23 (39.7)	19 (32.8)	
TOAST classification, n (%)				ns
Atherothrombotic	21 (17.7)	52 (43.7)	46 (38.6)	
Cardioembolism	8 (16.6)	17 (35.4)	23 (47.9)	
Small artery	6 (13.0)	20 (43.5)	20 (43.5)	
Other	8 (38.1)	8 (38.1)	5 (23.8)	
Undetermined	14 (31.1)	12 (26.7)	19 (42.2)	
Fazekas rating scale score (mean $\pm$ SD)*	3.1 $\pm$ 1.3	3.6 $\pm$ 1.5	3.5 $\pm$ 1.3	ns

Abbreviations: HbA1c, hemoglobin A1c; IQR, interquartile range; NG, normoglycemic; NIHSS, National Institutes of Health Stroke Scale; ns, nonsignificant; PD, prediabetes; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

* White matter hyperintensities.