original article

The association of diabetes with ischemic stroke and transient ischemic attacks in a tertiary center in Saudi Arabia

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BACKGROUND: Diabetes mellitus increases stroke risk 1.5 to 3 fold, particularly ischemic stroke. There is limited literature on the impact of diabetes on stroke patients in Saudi Arabia.

OBJECTIVES: Determine the association of diabetes on the presentation, subtypes, in-hospital complications and outcomes of ischemic stroke and transient ischemic attacks (TIA).

DESIGN: IRB approved, retrospective chart review.

SETTING: Tertiary care center.

PATIENTS AND METHODS: All adult patients with ischemic stroke or TIA aged 18 years or older admitted from January 2016 to December 2017 were included.

MAIN OUTCOME MEASURES: Stroke severity at presentation, stroke-related complications, discharge disposition and discharge modified Rankin Scale (mRS) in relation to diabetes.

SAMPLE SIZE: 802 patients.

RESULTS: Among 802 cases, 584 (72.8%) had diabetes; the majority (63.1%) were males. The mean age was younger in the non-diabetic stroke group (54.6 [15.5] years vs. 63.3 [9.9], *P*<.001). Hypertension (83.6% vs 49.1%, *P*<.001), dyslipidemia (38.9% vs. 28.9%, *P*=.009), prior stroke (27.7% vs. 19.3% *P*=.014), and ischemic heart disease (20.4% vs. 7.8%, *P*<.001) were more common in diabetic patients whereas smoking was more common (19.3% vs. 11.1%, *P*=.003) in the non-diabetic patients. The commonest subtype of stroke was large artery disease followed by small vessel disease. Both were more common in diabetic vs. non-diabetic patients (55.8% vs. 44%, *P*=.003), and (16.6% vs. 11%, *P*=.05) respectively. Diabetic stroke patients were more likely to have lacunar stroke (16.4% versus 9.2%, *P*=.009). TIAs occurred more commonly in the non-diabetic group (26.1% vs. 13.7%, *P*<.001). Non-diabetic patients had a better outcome (mRS score of 0-2) at discharge (62.4% vs. 45.9%, *P*=.002).

CONCLUSIONS: Almost three-fourth stroke patients were diabetic in our cohort. Diabetic stroke patients were older, had multiple vascular comorbid conditions, presented late to the hospital, and were likely to have more disability at the time of discharge. Large vessel atherosclerosis as well as lacunar infarctions were more common in diabetic stroke patients.

LIMITATIONS: Missing data about time of presentation in few patients, missing modified Rankin Scale score at discharge.

CONFLICT OF INTEREST: None.

Ischemic stroke is estimated to account for 75-80% of all stroke cases in Saudi Arabia.[1] Of the 7.4 billion people currently living in the world, an estimated 6.2 million lives are expected to be lost to stroke every year.[2] The prevalence of diabetes in patients with stroke has been estimated to be 28%.[3] Studies have indicated that diabetes mellitus is associated with 1.5-3 fold increase in risk for stroke, particularly cerebral infarction.[4] This excess risk is especially evident in women, and younger age groups.[5] A study published in 2011 found that 30% of 6024 Saudi subjects with a mean age of 50 years had diabetes mellitus.[6] An older study conducted in 1995-2000 with a larger population of 16917 Saudis between the ages of 30 and 70 years old found that the prevalence of diabetes was 23%.[7] A recent review found that Saudi males have higher prevalence compared to females but onset is earlier in females.[8] With increasing incidence and prevalence of diabetes, the risk of stroke is also expected to increase, particularly with the ageing population in Saudi Arabia.

Studies have shown that the presentation of stroke in diabetics differs from non-diabetics. There is a trend toward lacunar and atherothrombotic infarction in diabetics when compared to non-diabetics.[9] Additionally, age above 85 years, and presence of ischemic heart disease increased the risk of ischemic stroke in diabetic patients.[10]

Our study aimed to identify the differences between diabetics and non-diabetics with ischemic strokes or transient ischemic attacks (TIAs) in terms of presentation, in-hospital course, and outcome. It also aimed to identify the subtype and region of ischemic strokes.

PATIENTS AND METHODS

The study was a retrospective chart review, approved by the local institutional review board (IRB). All adult patients with ischemic stroke or TIA aged 18 years and above of both genders, admitted to the stroke unit at King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNGHA), Riyadh between January 2016 and December 2017 were included. Patients with intracerebral hemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis, and final diagnosis other than ischemic stroke or TIAs were excluded. Demographic, clinical and radiological data were collected in prespecified form. All data regarding the patient were collected from the patient's electronic record. Patients who had been diagnosed with diabetes mellitus in the past—either diabetes mellitus I or II—or had a recent (within 1 week of initial presentation) HbA1c ≥6.5% were labeled as diabetic in our study.[11] Patients with neurological deficits that lasted <24 hours and left no long-term disability or signs on imaging were diagnosed with TIA. Patients with neurological deficits lasting beyond 24 hours and with ischemic findings on imaging were diagnosed with stroke. Stroke subtype was determined based on the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification.[12] Stroke severity was assessed using both the NIHSS (National Institute of Health Stroke Scale) at initial presentation and discharge, and the mRS (modified Rankin Scale) at discharge and follow-up.[13] The follow-ups were conducted at intervals of 3 months, 6 months and 12 months. NIHSS is a standardized examination performed for acute stroke assessment, whereas modified Rankin Scale is the most commonly used tool to determine outcomes in stroke trials. Stroke region was identified using MRI images, and then distributed into three categories. The regions of the middle cerebral artery, anterior cerebral artery, posterior cerebral artery and internal carotid arteries were grouped under cortical strokes. The subcortical, borderzone and basal ganglia regions were grouped under subcortical strokes. Brainstem and cerebellar strokes in the basilar artery territory, cerebellar arteries territory, vertebral artery territory were grouped as infratentorial strokes. The strokes were divided into lacunar and non-lacunar based on size and vascular supply, when applicable. Subcortical and infratentorial ischemic regions that were <1 cm on MRI were labeled as lacunar. In-hospital complications that were assessed included; recurrent stroke, deep vein thrombosis or pulmonary embolism, decompressive surgery, seizures, bedsores, gastrostomy, myocardial infarction, sepsis, urinary tract infection, brain edema, pneumonia, tracheostomy, fall, and death.

The descriptive statistics are given as median and interquartile range for continuous variables with a non-uniform distribution and the categorical variables were presented as counts and percentages. The Pearson Chi-square or Fisher exact test was used to determine associations between the categorical variables for the outcome variable. A multiple logistic regression analysis was performed to assess the association between diabetes and mRS outcomes at discharge, infratentorial non-lacunar strokes, infratentorial lacunar strokes, lacunar strokes and non-lacunar strokes, adjusting for factors such as age, sex, smoking, dyslipidemia, hypertension, triglycerides, prior stroke, ischemic heart disease, and congestive heart failure. Odds ratios (ORs) with 95% confidence intervals (CIs) were expressed relative to a reference baseline category. A *P* value less than .05 was assumed statistically significant. The statistical software package IBM SPSS (Armonk, NY: IBM Corp) version 24) was used for statistical analysis.

RESULTS

Of 1249 patients admitted to the stroke unit between January 2016 and December 2017, 802 patients met the inclusion criteria, with a diagnosis of either TIA or ischemic stroke. Among the 802 patients, 63.1% were males, 72.8% were diabetics. The age and gender distribution, vascular risk factors and stroke region are presented in **Table 1**, comparing the diabetic stroke patients and non-diabetic stroke patients. Diabetic stroke patients were older than the non-diabetic stroke patients (*P*<.001). Several vascular risk factors including hypertension, dyslipidemia, prior stroke and ischemic heart disease were more common in the diabetic stroke patients, whereas smoking was less common. A total of 54 patients received thrombolysis during the study period. We did not compare the patients who received thrombolysis to those who did not receive thrombolysis. **Table 2** compares the etiological classification of strokes in the diabetic stroke group and non-diabetic stroke group. TIAs occurred more commonly in the non-diabetic stroke group prior to stroke (*P*<.001). The most common subtype of stroke was large artery disease, accounting for 52.6% of all strokes, followed by small vessel disease. Both were more common in the diabetic stroke group than the non-diabetic stroke group (55.8% vs. 44%, *P*=.003), and (16.6% vs. 11%, *P*=.05) respectively. The diabetic stroke patients were more likely to have lacunar stroke (16.4% versus 9.2, *P*=.009). Multiple logistic regression analysis (**Table 3**) showed that the odds of having lacunar stroke were almost twice as common in the diabetic stroke patients (OR 1.960, 95% CI 1.097–3.501, *P*=.023). TIAs occurred more commonly in the non-diabetic stroke patients (26.1% vs. 13.7%, *P*<.001). When the strokes were classified according to location, cortical strokes were the most common type of stroke, accounting for 64.6% of all strokes. Interestingly, both non-lacunar and lacunar infratentorial infarctions were more common in the diabetic stroke patients, (*P*=.028, and *P*=.012 respectively) (**Table 1**).

In our sample, significantly more of the non-diabetic stroke patients presented to the emergency room within 3 hours of symptom onset (*P*=.003), whereas almost 38% of diabetic stroke patients presented after 24 hours of symptoms onset. The clinical presentation did not differ between the two groups, except for aphasia which was more common in the non-diabetic stroke group (14.2% versus 7.9%; *P*=.007). The stroke severity at presentation did not differ among the diabetic and non-diabetic stroke patients (**Table 1**). Multiple regression analysis showed that moderate-to-severe disability or death (mRS >2) was more common in the diabetic

Table 1. Demographics, stroke severity, risk factors, time of presentation and stroke region in diabetic and non-diabetic patients (n=802).

Demographics	Diabetic (n=584)	Non-diabetic (n=218)	*P* value
Age (years)[a]	64 (57-71)	53 (44-68)	<.001
Sex			
Male	371 (63.5)	135 (61.9)	.676
Female	213 (36.5)	83 (38.1)	
Stroke severity	333 (57)	132 (60.6)	.759
NIHSS at presentation n (%)	140 (24)	51 (23.4)	
	46 (7.9)	13 (6)	
	12 (2.1)	4 (1.8)	
Risk factors			
Hypertension	488 (83.6)	107 (49.1)	<.001
Dyslipidemia	277 (38.9)	63 (28.9)	.009
Atrial fibrillation	51 (8.7)	14 (6.4)	.283
Smoking	65 (11.1)	42 (19.3)	.003
Prior stroke	162 (27.7)	42 (19.3)	.014
Valvular heart disease	13 (2.2)	4 (1.8)	.732
Ischemic heart disease	119 (20.4)	17 (7.8)	<.001
Congestive heart failure	32 (5.5)	3 (1.4)	.011
Known carotid disease	5 (0.9)	2 (0.9)	.935
Peripheral vascular disease	9 (1.5)	1 (0.5)	.301
Other	53 (9.1)	37 (17.1)	.086
Stroke region[b]			
Cortical	379 (64.9)	139 (63.8)	.765
Subcortical non-lacunar	115 (19.7)	40 (18.3)	.668
Subcortical lacunar	70 (12)	18 (8.3)	.133
Infratentorial non-lacunar	98 (16.8)	23 (10.6)	.028
Infratentorial lacunar	27 (4.6)	2 (0.9)	.012
Infarct type[c]			
Lacunar	96 (16.4)	20 (9.2)	.009
Non-lacunar	401 (68.7)	138 (63.3)	.150
Duration of symptoms at presentation[d]			
<3 hours	138 (26.3)	75 (36.2)	.003
3-6 hours	71 (13.5)	37 (17.9)	
6-24 hours	116 (22.1)	42 (20.3)	
>24 hours	200 (38.1)	53 (25.6)	

Data are n (%) or [a]median (IQR). [b]Some patients are counted twice because of stroke in more than one region; [c]Patients with TIA and no imaging data were excluded from non-lacunar; [d]Many patients had no data on time of presentation, thus the total is less than 100%

Table 2. Comparison of TIAs and strokes according to the TOAST classification in diabetic and non-diabetic patients.

TOAST Classification	Diabetic (n=584)				Non-diabetic (n=218)				*P* value (diabetic versus non-diabetic)
	Total	Male	Female	*P* value	Total	Male	Female	*P* value	
Transient ischemic attack	80 (13.7)	45 (12.1)	35 (16.4)	0145	57 (26.1)	32 (23.7)	25 (30.1)	.295	<.001
Cardioembolism	50 (8.6)	29 (7.8)	21 (9.9)	.396	22 (10.1)	10 (7.4)	12 (14.5)	.093	.500
Large artery stroke	326 (55.8)	218 (58.8)	108 (50.7)	.059	96 (44)	68 (50.4)	28 (33.7)	.016	.003
Small vessel disease	97 (16.6)	61 (16.4)	36 (16.9)	.886	24 (11)	13 (9.6)	11 (13.3)	.407	.050
Other determined etiology	5 (0.9)	4 (1.1)	1 (0.5)	.657	6 (2.8)	3 (2.2)	3 (3.6)	.676	.079
Undetermined etiology	16 (2.7)	10 (2.7)	6 (2.8)	.931	11 (5)	8 (5.9(	3 (3.6)	.539	.107

Data are n (%).

Table 3. Three multiple logistic regression analyses with modified Rankin Scale (0-2 vs 3-5 or death), presence of lacunar stroke, and presence of non-lacunar stroke as dependent variables.

Dependent variables	Independent variables[a]	OR	95% Confidence Interval	*P* value
Modified Rankin Scale score >2 at discharge				
	Diabetic vs. non-diabetic	1.793	1.074 – 2.992	.026
	Age >65 years or less	1.613	1.061 – 2.450	.025
Lacunar strokes				
	Diabetic vs. non-diabetic	1.960	1.097 – 3.501	.023
Non-lacunar strokes				
	Hypertension vs. no hypertension	1.736	1.151 – 2.618	.009
	Ischemic heart disease vs. no ischemic heart disease	1.823	1.068 – 3.111	.028

[a]Statistically significant variables. modified Rankin Scale summary: *P*=.001, Nagelkerke R-square=.201; Lacunar strokes summary: *P*=.292, Nagelkerke R-square=.029; Non-lacunar strokes summary: *P*=.015, Nagelkerke R-square=.044.

stroke group (OR 1.793, 95% CI 1.074–2.992, *P*=.026). Age greater than 65 years was also a predictor of higher morbidity or death at discharge (OR 1.613, 95% CI 1.061–2.450, *P*=.025) (**Table 3**). Little over 2% of patients in both groups died in hospital, with no significant differences in discharge disposition (**Table 4**).

Stroke-related complications did not differ significantly between diabetic stroke patients and the non-diabetic stroke patients. Overall, 41.8% diabetic stroke patients had stroke-related complications compared to 36.2% of the non-diabetic stroke patients (*P*=.155). The common complications included pneumonia (4.8% in the diabetic group versus 4.6% in non-diabetic), gastrostomy tube placement (4.3% versus 2.8%), urinary tract infections (3.8% versus 4.1%) and tracheostomy tube placements (3.1% versus 2.3%).

DISCUSSION

Diabetes is considered one of the important risk factors for ischemic stroke. A recent review looking at 10242 patients estimated that 37.5% of ischemic stroke patients in the Arab world were diabetics with very few studies reporting more than 50% diabetics among the stroke patients.[14] In our cohort, we included all patients with ischemic stroke during the study period, of whom 72.8% were diabetics, which is much higher frequency than any previously reported study. Only one study has reported a higher frequency of 78.5% diabetics among

stroke patients.[15] The number of diabetic stroke patients is likely to increase with the projected increase of diabetes worldwide by 69% in developed countries and 20% in developing countries.[16] In Saudi Arabia, diabetes affects 30% of the population which is much higher than the 9.4% in USA, 9.3% in Canada, 7.3% in France, and 10% in Spain.[17-19] Thus, Western populations are expected to have a much lower percentage of diabetic stroke patients than Saudi Arabia.

Diabetes alone is not a good indicator of metabolic state, as blood sugar levels are dependent on patient factors such as compliance to medication and regimen. For that reason, the HbA1c levels were looked at to determine if the diabetic stroke patients had good control of their disease. Among the diabetic patients in our cohort, only 6% of patients had an HbA1c <6.5% measured within a week of presentation and 83% had an HbA1c ≥6.5%; which may suggest that poor control of diabetes may be the reason for such high numbers. Further studies into this with cut off points such as 7-7.9%, 8-8.9% and ≥9% may help to better delineate the level of HbA1c at which stroke occurrence spikes. Although studies have shown that reduction of blood glucose levels reduces the risk of cardiovascular events in general including myocardial infarction, stroke and congestive heart failure combined by 8.6 events per 5.6 years; more studies analyzing the direct effect of blood glucose on stroke as a dependent variable are needed.[20] The direct impact of strict diabetic control on stroke recurrence is controversial, and it has been shown that controlling blood glucose levels in the immediate post-stroke period did not improve patient outcomes.[21]

The younger mean age of our non-diabetic stroke patients is an interesting finding as it does not match with the previously published literature. A cohort study consisting of 244 532 patients in the UK found that diabetic stroke patients were younger than the non-diabetic stroke patients at the time of stroke, in contrast to our findings.[5] On the other hand, a Spanish study showed no significant difference between the mean ages of the two groups.[10] Similarly, a local study published in Saudi Arabia in 2017 also did not find any significant age difference in diabetic and non-diabetic stroke patients.[9] Stroke at a younger age is mostly attributed to etiologies such as dissection of the internal carotid artery or risk factors like thrombophilia and smoking. Smoking is the only risk factor that was significantly more prevalent in the non-diabetic group in our cohort, being almost twice as common, and may have played a role in the earlier incidence of stroke. Moreover, in the prior Saudi study, smoking was less prevalent and was

Table 4. Presentation severity, discharge disposition and discharge outcomes among diabetics and non-diabetics.

Scale	Diabetic (n=584)	Non-diabetic (n=218)	*P* value
Admission NIHSS score n (%)			
0-5	333 (57)	132 (60.6)	.759
6-15	140 (24)	51 (23.4)	
16-24	46 (7.9)	13 (6)	
>24	12 (2.1)	4 (1.8)	
NIHSS score at discharge			
0-5	296 (50.7)	132 (60.6)	.503
6-15	64 (11)	19 (8.7)	
16-24	16 (2.7)	7 (3.2)	
>24	7 (1.2)	4 (1.8	
Discharge disposition			
Death	12 (2.1)	5 (2.3)	.738
Long-term facility or still admitted at 3 months	8 (1.4)	2 (1)	
Discharged home	497 (85.1)	185 (84.9)	
Discharged to inpatient rehabilitation	33 (5.7)	10 (4.6)	
Transfer to another hospital	7 (1.2)	1 (0.5)	
Discharged against medical advice	11 (1.9)	7 (3.2)	
Modified Rankin Scale score at discharge			
0-2	268 (45.9)	136 (62.4)	.002
3-6	179 (30.7)	47 (21.6)	
Not available	137 (23.4)	35 (16.0)	
mRS score at 3 months			
0-2	40 (6.8)	20 (9.2)	.464
3-6	33 (5.6)	11 (5.0)	
Not available	511 (87.5)	187 (85.8)	
mRS score at 6 months			
0-2	24 (4.1)	6 (2.7)	.490
3-6	28 (4.8)	13 (6.0)	
Not available	532 (91.1)	199 (91.3)	
mRS score at 1 year			
0-2	16 (2.7)	3 (1.4)	.082
3-6	26 (4.5)	13 (6.0)	
Not available	542 (92.8)	202 (92.6)	
Stroke-related complications	244 (41.8)	79 (36.2)	.155

Data are number (%). NIHSS – National Institute of Health Stroke Scale

not significant in their non-diabetic group, which may have mitigated the effect of smoking.[9]

Transient ischemic attacks, as the first presentation of cerebrovascular disease, were also more common in our non-diabetic stroke patients. This has no clear explanation, although it is possible that diabetic stroke patients are more likely to attribute their symptoms to a fluctuation in their blood sugar and try to self-treat at home, instead of urgently seeking medical care. In our diabetic stroke group, hypertension, dyslipidemia, prior stroke, and ischemic heart disease were all significantly more prevalent than in the non-diabetic group (in descending order of prevalence). These results are similar but not identical to two other studies that found that prior stroke and hypertension were more common in diabetic patients with stroke.[5,10] Poorly controlled diabetes may contribute to other vascular risk factors as well and controlling blood glucose levels may be helpful in reducing stroke by controlling other vascular risk factors.

A large number of our patients had large vessel disease. One of the reasons for this finding may be that almost all patients get CT angiogram or MR angiogram; hence, large vessel disease is recognized more. Carotid artery disease is uncommon in our population as previously reported.[22] The cortical region was the most common site of infarction in both populations, probably due to the high prevalence of large artery atherosclerosis in general. Although infratentorial infarctions were relatively uncommon, they were significantly more common in diabetics. When comparing lacunar and non-lacunar infarctions, the lacunar infarctions were also significantly more common in diabetics. The literature has previously reported that diabetes may be associated with small vessel disease. In our cohort, the *P* value of .05 was of borderline statistical significance.[9,10,22] However, the results of our study showed diabetes as a significant predictor of lacunar infarctions. Additionally, ischemic heart disease and hypertension, were significant predictors of lacunar infarctions in our cohort.

Old age and diabetes were independent predictors of poor outcome at discharge. People older than 65 years of age, and those who had diabetes were significantly more likely to be discharged with mRS of 3-5 (moderate-to-severe disability). Unfortunately, long-term follow up was not available in a large proportion of patients, hence a definitive impact of diabetes on long-term outcome could not be determined. One of the potential reasons for poor outcomes in diabetic patients could be late arrival to hospital, where 38% of our diabetic patients presented beyond 24 hours of symptoms onset and hence lost the chance of thrombolytic therapy or acute intervention.

One of the limitations of our study was that it was retrospective. Some of the data including HbA1c results, time of arrival to the emergency room, and NIHSS at presentation were not available for all patients. Incomplete documentation or missing mRS scores at discharge and follow up were also a limitation in our study. Because our center caters to acute care of all patients who come to the emergency room, but provides continued care only to those who are registered as eligible in the system, many patients did not follow up in the outpatient clinic, which also affected the assessment of the impact of diabetes on long-term outcomes.

In conclusion, diabetes was present in almost three-fourths of our stroke patients, a number much higher than previously reported. Diabetic stroke patients were older and were likely to have poorer discharge outcomes. Most had poorly controlled diabetes. Concomitant vascular risk factors were also more common in the diabetic stroke patients, except smoking. Large vessel atherosclerosis was common in our cohort, and lacunar infarctions were more common in diabetic stroke patients. Diabetic stroke patients were likely to have delayed presentation to hospital.

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