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Original Article

The Impact of Hyperglycemia on Stroke Outcomes in Patients with and without Diabetes

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Abstract

Introduction: Diabetes mellitus is a well-established independent risk factor for the development of stroke. It increases stroke risk by about fourfold. Information is scarce on the prevalence of stroke in the Gulf region. A systematic review of stroke epidemiology in the Middle East reported an increase in stroke cases over the last decade. **Objectives:** We aimed to examine the relationship between adverse stroke outcomes and dysglycemia. **Patients and Methods:** In this observational, retrospective, cross-sectional study, we recruited 496 patients with a clinical and radiological stroke diagnosis. We compared the length of hospital stay (LOS), inhospital mortality, and 30-day stroke readmission among those with no diabetes, prediabetes, and diabetes. **Results**: A total of 496 patients were eligible for the inclusion in the study. They were subdivided into three main categories based on their glycemic status according to the Hemoglobin A1c values at presentation. nondiabetes (190), prediabetes (117) and diabetes (189). The mean age was 57 years, with a higher proportion of males ($n = 356$) than females ($n = 140$). There were proportionally more ischemic strokes ($n = 350$) than hemorrhagic strokes ($n = 147$). The mean LOS was 5.0 days for all patients, irrespective of their glycemic status. Inhospital mortality was 4%, with slightly higher mortality (5.3%) in the group with diabetes; however, this was not statistically significant. Glycemic status did not seem to impact the stroke readmission at 3 or 6 months significantly. Furthermore, the proportion of patients readmitted within 30 days of discharge was not different between the three categories. **Conclusions:** Ischemic strokes occur in a much higher proportion in our patients with diabetes. Dysglycemia did not significantly impact stroke outcomes in our cohort.

Keywords: Diabetes, hemorrhagic cerebrovascular events, hyperglycemia, hypertension, ischemic cerebrovascular events, outcomes

Introduction

Diabetes is an established, independent risk factor for the development of stroke.[1] Diabetes mellitus poses about four times higher risk for stroke.[2] The mechanisms that contribute to this increased risk include direct vascular injury due to oxidative stress and a pro-thrombotic state associated with hyperglycemia.[3] Other risk factors such as hypertension, dyslipidemia, and obesity coexist in patients with diabetes frequently.[2]

The prevalence of diabetes in the Gulf region is reported to be among the highest globally, estimated at 19% in the adult population.[4] A recent systematic review on stroke epidemiology in the Middle East suggested an increase in stroke cases over the last decade.[5] However, there is limited information on the prevalence of strokes in the Gulf region or its relationship to glucose intolerance. Hence, we aimed to examine this relationship using the data from a busy tertiary center in the UAE.

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Patients and Methods

Study design

This was a retrospective review of the patient's electronic medical records from January to December 2019 to examine the relationship between stroke outcomes and dysglycemia.

Objectives

We aimed to (1) determine the percentage of stroke types in patients with and without diabetes, (2) determine the impact of hyperglycemia on the length of hospital stay (LOS), (3) determine the effect of hyperglycemia on in-hospital mortality, (4) determine the incidence of stroke recurrence at

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3 and 6 months in patients with and without hyperglycemia, and (5) determine the incidence of 30-day stroke readmission in patients with hyperglycemia.

Study population

We included patients with and without diabetes presenting with cerebrovascular events, both ischemic and hemorrhagic, in a tertiary care center in the UAE. We defined stroke based on clinical focal neurological signs confirmed by radiological imaging studies. We included all patients admitted with a clinical and radiological confirmed diagnosis of stroke (both ischemic and hemorrhagic under the care of medical teams). We excluded patients admitted with stroke who were eligible for thrombolytic therapy or required surgical intervention. Those patients were managed by the neurologists and neurosurgeons, respectively, in dedicated stroke units. The selection of patients for the study is highlighted in Figure 1, and the number of patients whose follow-up data was available at 1, 3, and 6 months is shown in Figure 2.

Data variables and outcomes

Hemoglobin A1c (HbA1c) was used as a marker of dysglycemia to categorize patients into three groups based on the American Diabetes Association criteria. These were classed as normal: Hba1c <5.7%, prediabetes: Hba1c 5.7%–6.4%, and diabetes: Hba1c: Equal to or above 6.5%.

We recorded demographic details and other contributory risk factors such as hypertension, history of ischemic heart disease, and smoking. The duration of hospital stay was calculated as the time from admission until discharge from the hospital. The adverse outcomes recorded include in-hospital mortality during the index admission, the incidence of stroke recurrence at 6 months and 1 year, and the incidence of readmission due to any other medical cause in the same group of patients in 30 days from the date of onset of the stroke.

Statistical analysis

Statistical analyses were carried out using the IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine the distribution of data. The mean ± standard deviation (SD) was described for variables with normal distribution and median (interquartile range [IQR]) for variables with skewed distribution among the continuous data. Descriptive statistics were used to summarize the data, which was presented as numbers (percentages), means (SD), as appropriate. As age, body mass index (BMI), and HBa1c follow a normal distribution, a comparative analysis was carried out using the Analysis of variance (Parametric) under the assumption of mean and SD.

LOS is a time factor and does not follow a normal distribution. Hence, a comparative analysis of LOS was carried out by the Kruskal–Wallis test (Non-parametric ANOVA) under the assumption of mean and IQR.

All categorical data were summarized by frequency and percentage, whereas the Chi-square test made comparison among groups. The outcome variables were compared by Fisher's exact test, as the standard Chi-square test is valid only if the cell frequency is above 5 years.

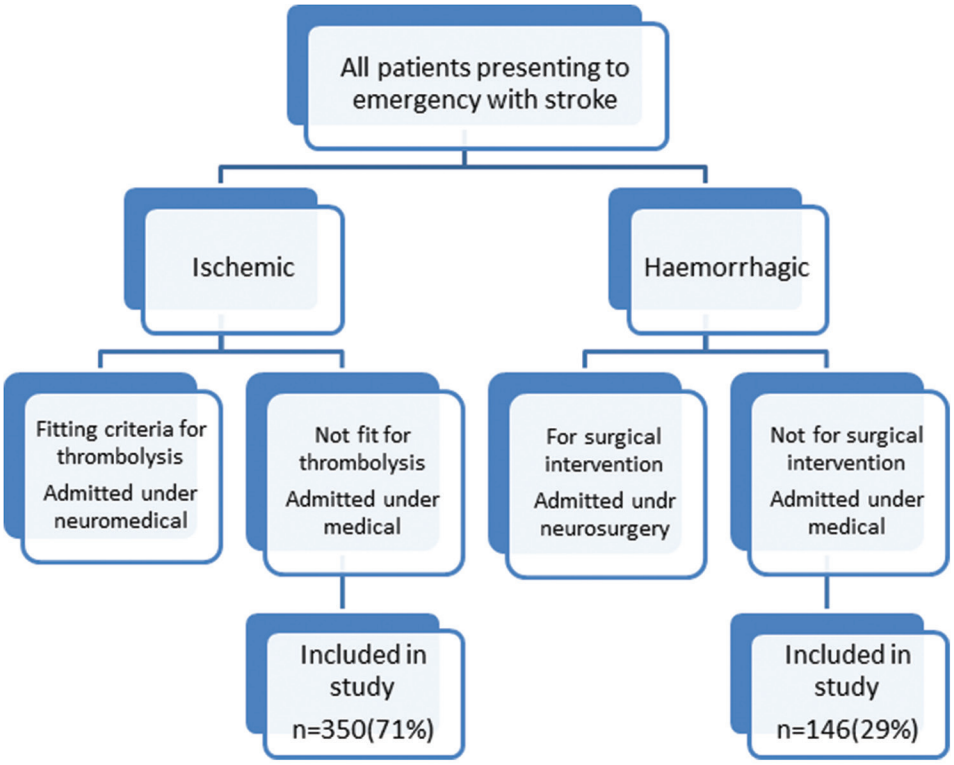

Figure 1: Patient selection flow chart

Results

A total of 496 patients were eligible for the inclusion in the study. They were subdivided into three main categories based on their glycemic status according to the Hba1c values at presentation: Nondiabetes (190), prediabetes (117), and diabetes (189). The mean age of whole cohort was 57 years, with a higher proportion of males (n = 356) than females (n = 140). There were proportionally more ischemic strokes (n = 350) than hemorrhagic strokes (n = 147).

A higher proportion of female patients, 42 (35.9%) were in the prediabetes group and the highest number of males, 143 (75.7%), in the diabetes category, as shown in Table 1.

Hypertension was found to be the most prevalent coexisting risk factor among the cohort. 74.2% of all stroke patients had hypertension.

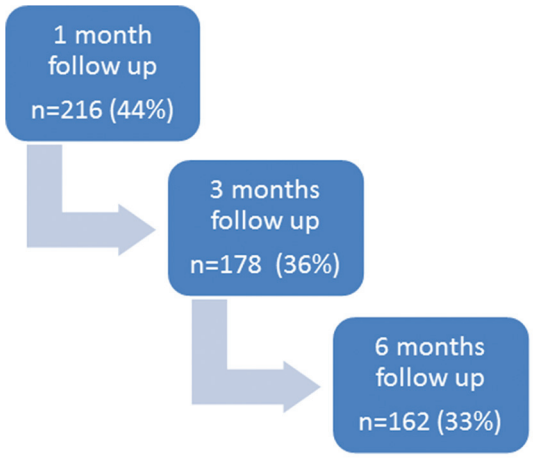

Figure 2: Follow-up of patients for outcomes

Smoking was evident in 22.2% of the cohort, with equal proportions among the three categories. 15% of the entire cohort had ischemic heart disease, with a higher proportion among those with diabetes. On average, the BMI was 27 across the three categories of patients.

The mean LOS was 5 days for all patients, irrespective of their glycemic status as shown in Figure 3. We subdivided the patients into two groups regarding the duration of hospital stay, those who stayed for 7 days or less and those who stayed for more than 7 days. Among all the three categories of patients, as shown in Table 2 and Figure 2, more than 50% of patients were discharged in <7 days.

In-hospital mortality was 4%, with slightly higher mortality (5.3%) in the group with diabetes; however, this was not statistically significant. The glycemic status did not seem to impact the stroke readmiss`ion at 3 or 6 months significantly. Furthermore, the proportion of patients readmitted within 30 days of discharge was not different between the three categories as highlighted in Table 3.

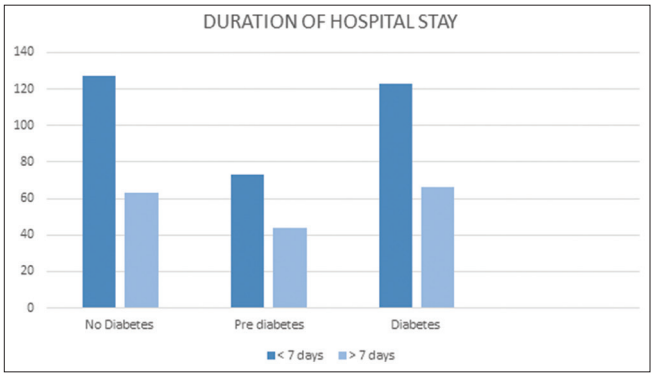

Figure 3: Hospital course according to glycemic status

Table 1: Patient demographics and baseline characteristics

Variable	Nondiabetes (n=190), n (%)	Prediabetes (n=117), n (%)	Diabetes (n=189), n (%)	Total (n=496), n (%)
Age (years), mean±SD	55.9±14.85	57.4±13.9	57.2±11.9	56.8±13.57
≤45	48 (25.3)	26 (22.2)	29 (15.3)	103 (20.8)
>45	142 (74.7)	91 (77.8)	160 (84.7)	393 (79.2)
BMI, mean±SD	27.5±10.0	27.7±10.6	27.7±8.7	27.6±9.5
Male	138 (72.6)	75 (64.1)	143 (75.7)	356 (71.8)
Female	52 (27.4)	42 (35.9)	46 (24.3)	140 (28.2)
UAE nationals	23 (12.1)	16 (13.7)	24 (12.7)	63 (12.7)
Expats	167 (87.9)	101 (86.3)	165 (87.3)	433 (87.3)
Hypertension				
Yes	142 (74.7)	88 (75.2)	138 (73)	368 (74.2)
No	48 (24.3)	29 (24.8)	51 (27)	128 (25.8)
Smoking				
Yes	40 (21.1)	24 (20.5)	46 (24.3)	110 (22.2)
No	150 (78.9)	93 (79.5)	143 (75.7)	386 (77.8)
History of IHD				
Yes	21 (11.1)	14 (12)	40 (21.2)	75 (15.1)
No	169 (89.9)	103 (88.0)	149 (78.8)	421 (84.9)
HbA1c (%), mean±SD	5.34±0.29	6.02±0.19	8.9±1.9	6.8±2.0

BMI: Body mass index, SD: Standard deviation, IHD: Ischemic heart disease, HbA1c: Hemoglobin A1c

Table 2: Hospital course according to glycemic status

Variable	Nondiabetes, *n* (%)	Prediabetes, *n* (%)	Diabetes, *n* (%)	Total, *n* (%)	*P*
LOS (days), median (IQR)	5 (2-10)	5 (2-10)	4 (3-11)	5 (2-10)	
LOS (days)					
≤7	127 (66.8)	73 (62.4)	123 (65.1)	323 (65.1)	0.73
>7	63 (33.2)	44 (37.6)	66 (34.9)	173 (34.9)	0.73

LOS: Length of hospital stay, IQR: Interquartile range

Table 3: Outcomes according to glycemic status

Variable	Nondiabetes (*n*=190), *n* (%)	Prediabetes (*n*=117), *n* (%)	Diabetes (*n*=189), *n* (%)	Total (*n*=496), *n* (%)	*P*
In hospital mortality during the same month	7 (3.7)	3 (2.6)	10 (5.3)	20 (4.0)	0.517
Number of patients readmitted within 30 days from discharge	7 (3.7)	6 (5.1)	9 (4.8)	22 (4.4)	0.822
Re-occurrence of stroke within a month N1	66, 2 (3)	61, 2 (3.3)	89, 1 (1.1)	216, 5 (2.3)	0.614
Recurrence of stroke with 3 months N1	79, 2 (2.0)	51, 0 (0.0)	78, 2 (2.5)	178, 4 (2.24)	0.410
Recurrence of stroke with 6 months N1	75, 0 (0)	41, 3 (6.7)	45, 3 (4)	162, 6 (3.7)	0.588

P value was calculated by Fisher's exact test. *P* value of <0.05 is considered statistically significant. Percentages are calculated based on the nonmissing elements (N1). *n*: Number of patients in each group. N1: Number of nonmissing elements in the respective category

Discussion

Diabetes is a multi-system disorder characterized by both microvascular and macrovascular complications. Cardiovascular and cerebrovascular diseases continue to pose a particular burden in patients with diabetes despite advances in diagnostic and therapeutic interventions. This concept is not a novel idea; however, when it comes to reporting outcomes and utilizing prognostic scales, the literature is fraught with considerable controversy as no single consensus protocol is available to unify the reporting of results.

Several organizations have attempted to define and standardize the reporting of clinical outcome measures for patients with strokes. Drozdowska *et al*. in a recent review of prognostic scales for acute stroke, summarizes the various problems encountered in trying to identify the most accurate methods of reporting predictive rankings in patients with strokes.[6]

Several studies have shown an association between comorbid diabetes and increased mortality**,** LOS, readmission rates, and worse functional and rehabilitation outcomes after stroke.[7] In contrast, other studies have reported no significant differences in poststroke outcomes between people with or without diabetes.[8]

Our study included a cohort of patients admitted for stroke management to a general medical unit. They were not eligible for thrombolytic therapy at the time of presentation and did not require any surgical interventions. As per our hospital policy, only those eligible for thrombolytic treatment or who require surgical intervention receive care in a dedicated stroke unit. Internists manage the rest in the general medical units.

The proportion of ischemic strokes (71%) was higher than those presenting with hemorrhagic events (29%) irrespective of the glycemic status. This observation appears to be a global phenomenon where ischemic events occur more frequently than hemorrhagic events. Ischemia is the most common stroke type, comprising 85% of all stroke presentations in the developed world.[9,10] El-Hajj *et al*. found that ischemic stroke was the most frequent type in the Middle East, followed by intracerebral hemorrhage and subarachnoid haemorrhage.[5]

We found a sex imbalance with a higher proportion of events, both ischemic and hemorrhagic, in males (72%) than females (28%). This observation is similar to other studies within our region, reporting 75% occurrence in males when compared to females.[5]

The number of expatriate patients, 433 (87.3%), far exceeded the number of UAE nationals, 63 (12.7%), in keeping with the country's population demographics. In general, the UAE population comprises approximately 80% expatriates and only 20% UAE nationals.

Our cohort's mean age was 57 years, slightly younger than what is reported in neighboring countries. Most patients presented in the sixth and seventh decade in a recent review on stroke outcomes in the Middle East.[5] In the same study, hypertension was the most common reported risk factor, followed by diabetes. In our cohort, 74% of the patients were hypertensive and 15% were found to have underlying ischemic heart disease.

BMI and smoking are other relevant risk factors for cerebrovascular events. In our study, the mean BMI was 27, and 22% of the cohort were identified as active smokers.

El-Hajj *et al*. reported a case fatality rate of 12%–32% within 1 month of stroke occurrence.[5] We found an in-hospital mortality rate of 4% in our cohort. Hyperglycemia impacted stroke outcomes negatively in patients with diabetes for both ischemic and hemorrhagic stroke types 9.[9,10] However, studies that have examined the effects of glucose-lowering in the setting of acute strokes have shown variable results.[11] In a prospective survey by Tziomalos, stress hyperglycemia did

not appear to be directly associated with the outcome of acute ischemic stroke.[12] However, a more recent review by Li *et al*., with over 8000 participants, reported that stress hyperglycemia, measured by glucose/HbA1c ratio, was associated with increased risk of severe neurological deficit and mortality within 1 year in the people with acute ischemic stroke.[13] We found that glycemic status did not seem to impact stroke readmission at 6 or 12 months significantly. Furthermore, the proportion of patients readmitted within 30 days of discharge was not different between the three categories based on their glycemic status.

Ying-Sung proposed that the predictive power of glycemic measures for poor neurological outcomes did not differ significantly between the normoglycemic patients and those with diabetes.[14] In a more recent publication, Guo *et al*. suggest that stress hyperglycemia may have a higher risk of stroke recurrence than previously diagnosed diabetes.[15]

We recognize some limitations of our study. First, it was a retrospective review in a single center with many patients lost to follow-up due to repatriation to their home countries (most patients were expatriates) and follow-up in other health care facilities. We did not report on the NIHSS stroke severity at presentation, which is an essential prognostic indicator of outcomes. We did not collect the data on other risk factors such as dyslipidemia or the presence of atrial fibrillation. Hyperglycemia was based on Hba1c measurements and not complemented by the presenting glucose levels on admission. Hba1c is well known to be unreliable in certain conditions, and this adds to the limitations. As it was a retrospective chart review, we could not ascertain the exact stroke etiology in all cases. Due to these limitations, the results of the study cannot be generalized to all stroke patients.

Conclusions

The relationship between hyperglycemia and stroke outcomes remains intriguing. Numerous studies conducted in different regions report variable and conflicting results. This might be explained by the studies' design, populations, and most importantly, perhaps the tools and measures used for reporting outcomes. This study adds considerable knowledge on the epidemiology of strokes in the UAE and is the first large observational study to report on the relationship between dysglycemia and stroke outcomes.

Our region needs extensive prospective studies that can better elucidate the intricate relationship between hyperglycemia and stroke outcomes. Diabetes remains a significant public health problem in our area, with rising numbers projected over the coming years. Increasing public awareness of the association between diabetes and strokes is essential to prevent the devastating consequences of strokes.

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Authors' Contributions

All authors contributed to the conception of the study, data collection and analysis, and drafting and revision of the manuscript. They all approved the final version of the manuscript.

Compliance with ethical principles

The study was conducted ethically as per the World Medical Association Declaration of Helsinki. The study protocol was approved by DSREC (Dubai Scientific Research Ethics Committee).Code Number: DSREC-02/2020_12.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability:

Data is available by reasonable requests to the corresponding authors.

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