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Glycemic State in Diabetic Patients during the Post-Stroke Recovery Phase

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Abstract

Background: Hyperglycemia is common in the early acute stroke phase especially in patients with diabetes. To the best of our knowledge, no study has evaluated the course of hyperglycemia in patients with diabetes during the post-stroke recovery phase.

Methods: It was an observational study conducted in Tabassom Rehabilitation Center for Stroke Patients, Tehran, Iran, 2018-2021. Forty-seven consecutive patients with diabetes and stroke were enrolled and included if at least 3 months had passed from their stroke . Any change in glycemic control before and after stroke was controlled by monitoring drugs used for diabetes treatment and laboratory results. To assess categorical variables, the Pearson chi-squared test was used. Quantitative variables before and after the stroke were analyzed by the paired sample t-test.

Results: The mean age was 63.6 ± 6.9 years, and 22 patients were women. The median time from occurrence of stroke to the first visit was 5 months and 6 days. Glycemic control improved among patients with diabetes during the post-stroke recovery phase. There was a significant decrease of 0.7 ± 1.3 % in HbA1c (P = 0.001). The number and the dose of drugs needed for diabetes treatment decreased. No significant correlation could be found between changes in HbA1c and weight.

Conclusion: Despite the initial increase in glycemia in patients with diabetes in the acute phase of stroke, glycemic control improves after stroke, and often, it is necessary to decrease diabetes drugs to prevent hypoglycemia. This topic is important and should be addressed by guidelines and institutions involved in the care of patients with diabetes and stroke.

Keywords: Diabetes, Glycemic Control, Rehabilitation, Stroke, Post-Stroke Recovery

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Introduction

Cardiovascular disease (CVD) is the leading global cause of death, and in 2019, nearly 18.6 million deaths were attributed to CVD (1). Of these, 6.6 million deaths were attributable to stroke and half of them were due to ischemic stroke (1) and stroke remains the second leading cause of death (2). The global prevalence of ischemic stroke in 2019 was 77.2 million people, whereas those of intracerebral hemorrhage and subarachnoid hemorrhage were 20.7 million and 8.4 million respectively (3).

In 2019, 463 million adults (20-79 years) were living with diabetes, and half of them were unaware of their diabetes (4). CVD risk is increased two to three times in people

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↑What is "already known" in this topic:
Stroke, as well as mortality following stroke, is increased in patients with diabetes and hyperglycemia is common in the early acute stroke phase and guidelines suggest treating hyperglycemia. However, there is no study evaluating the course of hyperglycemia in patients with diabetes after stroke during post-stroke recovery phase.

→What this article adds:
We observed that in patients with diabetes after a median of 5 to 6 months post-stroke, glycemic control improves, and often it is necessary to decrease diabetes drugs to prevent hypoglycemia. We think this topic is important and should be addressed by guidelines and institutions involved in the care of patients with diabetes and stroke.

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with diabetes (4, 5). Stroke, as well as mortality following stroke, is increased in patients with diabetes, and compared with nondiabetic patients, they are 2.9 times as likely to have a stroke (6). The median direct medical costs for 1 year after the onset of stroke were $27,000 (7). Prediabetes also has been linked to increased stroke risk (8) and considering that in 2019, 374 million adults (20-79 years) had impaired glucose tolerance (4), the importance of hyperglycemia as a modifiable risk factor, becomes more evident.

On the other hand, hyperglycemia is common in the early acute stroke phase (9) and this is not necessarily seen only in patients with previously diagnosed diabetes and prediabetes. It can occur as transient hyperglycemia in as much as 20 percent of stroke patients that can be completely normalized after the acute phase stroke (10). Even transient hyperglycemia is associated with worse post-stroke outcomes (11).

Although hyperglycemia during the acute phase of stroke is associated with poor outcomes, and guidelines suggest treating hyperglycemia (12), it has not been shown that intensive glucose control will result in a significant difference in favorable functional outcomes (13).

Many studies have assessed the hyperglycemia encountered during the acute phase of stroke and possible benefits obtained from proper control of it (14); however, the course of hyperglycemia in patients with diabetes after stroke during the post-stroke recovery phase is not clear and to the best of our knowledge, there is no study evaluating this issue. The purpose of this study was to extend our understanding of the glycemic state among patients with diabetes after the acute phase of stroke and especially during the rehabilitation period.

Methods

Study population

Between May 2018 and February 2021, forty-seven consecutive patients with diabetes and stroke scheduled for rehabilitation at "Tabassom Rehabilitation Center for Stroke Patients" in Tehran were enrolled in this study. Patients were included if they had a history of diabetes and at least three months had passed from their stroke. Patients were included in the study only if they had the lab test results regarding their glycemic state before the stroke and the results were written in the questionnaire obtained during the first visit. The mean duration of diabetes was 11.6 ± 6.2 years. This study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran. Written informed consent was obtained from all the patients.

Study protocol

This was an observational study. At the first visit, a questionnaire was filled out. Rouzbeh Kazemi M.D., and Mahsa Nazifi B.Sc., filled out the questionnaires. The questionnaire contained the patient's basic information including anthropometric indices and blood pressure, medical history, especially about diabetes, hypertension, and stroke, drug history especially diabetes and hypertension drugs, and available laboratory results. At the first visit, weight and height were measured but the weight before stroke was recalled by the patient or the relative accompanying the patient. The primary goal of the study was to see if there was any change in glycemic control of the patients before and after stroke. This was ascertained by monitoring any change in drugs used for control of diabetes and laboratory results (HbA1c& FPG) during the time before the stroke to visits performed in the Tabassom clinic. If the patient had a very recent lab result of Hb A1c and FPG tests, after obtaining consent from patients, the questionnaire was filled out on the very first visit. Otherwise, lab tests were requested and the questionnaire was completed on the next visit less than one month later.

Definition of terms

Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL or Hb A1c≥6.5% or taking anti-diabetic drugs, including oral agents or insulin. All of the patients in our study were according to the definition by WHO (World Health Organization) for stroke.15 WHO defines stroke as rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours, with no apparent cause other than of vascular origin (15, 16). Since all of our patients had an acute onset, we preferred this definition to that of the American Heart Association/American Stroke Association, which includes silent infarctions (16, 17).

Statistical analysis

Considering a power of 80% (β = 80%), a P value of <0.05 (α = 0.05), and an effect size of 0.5 (medium effect size), the minimum sample size using the method for before/after studies was calculated to be 32 persons. Since no similar study has been performed previously, the SD of the change in outcome (Hb A1c) was calculated using the SD and correlation in the population (SD = 1).

The continuous data were expressed either as mean (standard deviation (SD)) or median (interquartile range (IQR)) and the categorical data were expressed as numbers (percentage). To assess categorical variables, the Pearson chi-squared test was used. Quantitative variables before and after the stroke were analyzed by the paired sample t-test. Two-tailed $P < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Characteristics of the study population

A total number of 47 participants were included in this study. The mean age of participants was 63.6 ± 6.9 years (range: 47-81 years), and 22 patients (47%) were women. One patient was underweight (BMI: 17 Kg/m^2) and one-third (15 patients) had normal BMI (BMI: 18.5 – 24.9 Kg/m^2). The rest were either overweight (BMI: 25.0 – 29.9 Kg/m^2) or obese (BMI≥30 Kg/m^2) (mean ± SD: 27.00 ± 4.46 Kg/m^2, range: 17 – 36 Kg/m^2) (Table 1). As mentioned, all the patients had type II diabetes, and the mean duration of diabetes was 11.6 ± 6.2 years. Eleven patients (23%) had a hemorrhagic stroke, and the rest had an ischemic stroke. We did not have enough data about stroke

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Table 1. General characteristics of study participants at baseline

Variable	Overall (N= 47)
Age, mean (SD), year	63.62 (6.86)
Sex, No. (%)	
Male	25 (53.2)
Female	22 (46.8)
BMI, mean (SD), kg/m^2	27.00 (4.46)
BMI, No. (%)	
Underweight	1 (2)
Normal	15 (32)
Overweight or obese	31 (66)
The duration of diabetes, median (IQR), Year	10 (7.5-15)
Weight, mean (SD), kg	78.3 (13.4)

severity; however, none of our patients were fed through a nasogastric tube or percutaneous endoscopic gastrostomy. The median time from the occurrence of the stroke to the first visit was 5 months and 6 days (IQR: 113-317 days, mean ± SD: 219 ± 142 days). There was a significant weight loss of 6.4 ± 7.5 Kg in the study population during this period ($P < 0.0001$). The mean weight of the participants before the stroke was 78.3 ± 13.4 Kg and at the entry to the study (after the stroke) was 71.8 ± 13.9 Kg. At the entry to the study, patients had lost 8.3 ± 9.4 percent of their weight measured before the stroke. This can be translated to a decrease in BMI of 2.1 ± 3.5Kg/m^2.

Primary end-point

Glycemic control is defined as a decrease in the glycated hemoglobin A1c (HbA1c) improved among patients with diabetes during the post-stroke recovery phase. There was a significant decrease of 0.7 ± 1.3 % in HbA1c ($P = 0.001$) in the study population. The Mean HbA1c of the participants before stroke was 7.7 ± 1.1 % and at the entry to the study (after stroke) was 7.0 ± 1.1 % (Table 2). Fasting plasma glucose (FPG) as another indicator of glycemic control also improved. There was a significant decrease of 47 ± 70 mg/dL in FPG ($P < 0.0005$). The mean FPG of the participants before stroke was 183 ± 67 mg/dL and at the entry to the study (after stroke) was 136 ± 41 mg/dL. As can be seen in Table 2, despite a decrease or no change in HbA1c and FPG. Usually, the dose and the number of drugs used for treating diabetes are decreased. There was no difference in men or women regarding HbA1c or FPG change ($P = 0.312$ & $P = 0.316$, respectively). Type of stroke (ischemic or hemorrhagic) also had no significant relation with HbA1c or FPG change ($P = 0.351$ & $P = 0.576$, respectively) (Table 3).

Interestingly, despite a significant weight loss, no significant correlation could be found between change in HbA1c and change in net weight loss, percent of body weight loss, or decrease in BMI as continuous variables; also, there was no significant difference in HbA1c change in patients with ≥5% body weight loss and those with <5% body weight loss (weight considered as a categorical variable). When participants were categorized into those with ≥10% body weight loss and those with <10% body weight loss, again, no significant difference in HbA1c change was observed between the two groups. There was a weak significant correlation between change in fasting plasma glucose and change in net weight loss, percent of body weight loss, and decrease in BMI (R = 0.36 & $P = 0.019$, R = 0.33 & $P = 0.033$, and R = 0.34 & $P = 0.025$ respectively).

Table 2. Mean HbA1C and FPG of the participants before and after stroke

Variable	Before	After	*P*-Value
Hb A1c	7.73 ± 1.13	7.01 ± 1.07	0.001
FPG	183.36 ± 67.20	136.59 ± 41.17	< 0.001

Discussion

This study shows that in patients with diabetes who have experienced a stroke, after a median of 5 to 6 months, glycemic control has improved, and the dosage and the quantity of medications employed to manage diabetes reduced.

Several possible reasons can explain this observation. Weight loss increases the likelihood of diabetes control and even can result in diabetes regression. In the DiRECT trial, the likelihood of diabetes remission increased with increasing weight loss in the setting of primary care for 6 years. In those who lost >15 Kg, 10-15 Kg, 5-10 Kg, 0-5 Kg, and those who gained weight, 86%, 57%, 34%, 7%, and 0% respectively achieved remission of diabetes (18) indicating the importance of non-pharmacological approaches in diabetes management (19). Our patients had a significant weight loss of 6.4 ± 7.5 Kg; however, this weight loss could not explain the improvement in glycemic control and no significant correlation could be found between them. To further investigate the role of weight loss, we evaluated HbA1c or FPG change by categorizing patients to those with lost >15 Kg, 10-15 Kg, 5-10 Kg, 0-5 Kg weight loss, and again no statistically significant difference between groups could be found although it is possible that our study did not have enough power to assess this due to its small sample size.

It is also possible that other mechanisms are responsible for the improved glycemic control observed during the post-stroke recovery phase. Exercise can decrease the relative risk of diabetes and improve glucose tolerance in patients with diabetes and even cause remission of diabetes (20). Certainly, we cannot say that our patients had more physical activity compared to pre-stroke time, but it can be hypothesized that concerning their deteriorated fitness after stroke, they had more physical activity during their rehabilitation in the clinic and at home and this may have led to improved glycemic control. Unfortunately, we could not measure the number of calories consumed during physical activity by a standard method and more studies are needed. Unfortunately, in Iran, it is not possible for everyone to attend rehabilitation centers after a stroke due to costs and shortcomings of the support system and it can be assumed that those participating in our study are probably more motivated and belong to a higher socioeconomic class and after stroke can afford a healthier lifestyle and a combination of mentioned actions has resulted in improved glycemic control.

Complex pathways in the central nervous system are implicated in the development of diabetes (21-23). We could not find any study on the impact of stroke on patients with

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Table 3. Changes in HbA1c, FPG, and drugs used for diabetes treatment before and after stroke

Patient	Age	Sex	years with DM	FPG before	FPG after	Hb A1c before	Hb A1c after	Drugs before	Drugs after
1	58	M	15	200	165	8.5	7.2	Insulin 20	Glibenclamide 5, Acarbose 100
2	74	M	20	112	133	6.6	7.1	Gliclazide 80, Metformin 1000	Gliclazide 80, Metformin 1000
3	70	M	25	308	140	.	.	Insulin 6, Glibenclamide 2.5, Metformin 1000	Insulin 6, Glibenclamide 2.5, Metformin 1000
4	50	M	5	200	166	7.6	6.6	Metformin 1000	Sitagliptin 100
5	71	F	10	140	127	7.6	5.9	Insulin 28, Metformin, Sitagliptin	Metformin, Sitagliptin
6	58	M	15	250	101	7.2	6.2	stopped drugs by himself	Metformin 1000, Sitagliptin 100
7	55	F	12	.	142	7.6	6.9	Insulin 46	Insulin 26
8	59	M	4	.	131	8	7.2	Insulin 16	Glibenclamide 10
9	64	F	6	150	132	7.9	7.1	Insulin 10, Glibenclamide 5, Metformin 1000	Metformin 1000
10	66	F	8	150	141	7.4	7.5	Insulin 20	Insulin 24
11	66	F	22	.	112	7.2	6.8	Insulin 36	Insulin 28
12	67	M	18	250	173	6.1	6.6	Insulin 14, Metformin 1000, Sitagliptin 100	Insulin 14, Gliclazide 80
13	64	F	16	200	109	7.8	6.1	Insulin 30	Insulin 30
14	60	F	4	110	132	6.2	6.9	Insulin 12	Metformin, Glibenclamide
15	55	M	15	140	138	6.6	6.8	Gliclazide 80, Metformin 1000	Gliclazide 80, Metformin 1000
16	63	F	12	137	130	6.6	6.4	Metformin 2000, Sitagliptin 100	Metformin 500
17	68	F	7	140	120	7.4	6.7	Insulin 18	Insulin 16
18	58	F	20	142	131	6.8	6.7	Insulin 20	Insulin 16
19	63	M	10	135	126	7.5	7.1	Metformin 1000, Sitagliptin 100	Metformin 1000
20	63	M	10	131	139	6.3	6.8	Gliclazide 160, Metformin 1000, Sitagliptin 100	Gliclazide 160, Metformin 1000, Sitagliptin 100
21	72	M	15	182	159	8.3	7.9	Insulin 24	Gliclazide 160, Metformin 1000
22	61	F	5	160	87	7.4	6.8	Glibenclamide 10	Glibenclamide 10
23	62	M	15	138	129	7.2	6.8	Metformin 1000	Metformin 1000
24	57	F	9	200	101	8.1	6.6	Gliclazide 320	Metformin 500, Sitagliptin 50
25	57	M	8	200	135	9.7	6.4	Metformin 1000	Gliclazide 160
26	68	M	10	229	120	9.2	5	Gliclazide 160, Metformin 1000	Gliclazide 160, Metformin 1000, Sitagliptin 100
27	65	M	15	99	83	5.4	5.5	Gliclazide 160, Metformin 1000, Sitagliptin 100	Gliclazide 80, Empagli-flozin 10
28	59	F	6	141	153	6.9	7.1	Gliclazide 160, Metformin 1000	Gliclazide 160, Metformin 1000
29	67	F	10	115	124	6.6	6	Metformin 1000	Metformin 1000
30	53	M	7	218	122	9.7	5.6	Metformin 1000, Sitagliptin 100	Metformin 1000, Sitagliptin 100, Empagli-flozin 10

diabetes and its effect on these pathways. However, based on our findings, It is expected that interesting studies will be conducted in this field. Our study as the initial study, represents the need to reduce anti-diabetic medications during the post-stroke recovery phase due to improved glycemic control. Nevertheless, it is imperative to mention several limitations of our study. Firstly, it was a small-scale study founded on our observations and follow-up of diabetic stroke patients. This necessitates validation through more extensive studies. Secondly, the elimination of confounding factors was prevented because of the study's design and it is necessary for studies with a more powerful design. The most important confounding factor is weight. We considered the weight but other factors like diet and exercise are not easily assessable and need a prospective cohort study. All of the patients were recommended to visit a dietitian and get a diet consultation but we do not have enough data on how they were compliant with the recommendations. Another important issue is the variability of time passed from stroke to the entry to the study. We were not able to control for this variation and further studies are needed. The reason behind the observed enhancement in glycemic control among diabetic patients during the post-stroke recovery phase remains unclear. Nonetheless, whatever the underlying cause may be, it holds significant implications for patient safety and for healthcare providers and institutions, prompting a need for a well-thought-out pharmacological strategy to mitigate the risk of hypoglycemia and its associated adverse outcomes.

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Table 3. Continued

Patient	Age	Sex	years with DM	FPG before	FPG after	Hb A1c before	Hb A1c after	Drugs before	Drugs after
31	81	M	35	157	159	6.9	7.3	Insulin 54	Insulin 56
32	72	F	.	158	155	7.1	7.9	Insulin 28	Insulin 42
33	66	M	17	210	117	9.5	9.9	Metformin 1500	Metformin 1000, Sitagliptin 100, Empagliflozin 10
34	63	F	11	122	121	6.9	5.3	Glibenclamide 20, Metformin 1500	Glibenclamide 10, Metformin 1500
35	76	M	15	270	138	8.4	6.9	Glibenclamide 10, Metformin 1000	Glibenclamide 10, Metformin 500
36	47	M	8	170	80	8.4	7.6	Glibenclamide 10, Metformin 1000	Glibenclamide 5, Metformin 1000
37	74	F	10	278	134	10	7.4	No drugs?!	Metformin 1500
38	72	F	7	126	299	7.7	10.2	Metformin 500, Sitagliptin 50	Insulin 51, Metformin 500, Sitagliptin 50
39	61	F	15	400	271	.	8.9	Metformin 1000	Insulin 52
40	65	M	6	110	93	6.2	7.1	Metformin 1500	Metformin 1000, Empagliflozin 10
41	61	F	10	370	99	9.2	7.6		
42	65	M	10	130	101	7.4	6.7	insulin 75	insulin 42
43	68	F	9	232	179	9.7	8.8	Metformin 500, Sitagliptin 50	Metformin 500, Sitagliptin 50
44	65	M	10	220	130	8.8	7	insulin 34	insulin 22
45	58	F	7	147	170	9.1	9.9	Glibenclamide10, Metformin 1500	Gliclazide 80, Empagliflozin 10
46	56	M	6	213	157	9.5	6.2	Metformin 1000, Sitagliptin 100	Gliclazide 80, Metformin 1000, Empagliflozin 10
47	67	M	3	178	91	7.9	7.7	Metformin 500	Metformin 1000

Conclusion

In conclusion, despite the initial increase in glycemia in patients with diabetes in the acute phase of stroke, glycemic control improves as early as five months after stroke, and often it is necessary to decrease diabetes drugs to prevent hypoglycemia. We think this topic is important and should be addressed by guidelines and institutions involved in the care of patients with diabetes and stroke.

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Conflict of Interests

The authors declare that they have no competing interests.

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