Original Article

Diabetes mellitus type 2 impedes functional recovery, neuroplasticity and quality of life after stroke

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Abstract

Objectives: The recovery after stroke depends on the resolution of brain edema and neuroplasticity. The comorbidities associated with stroke such as type 2 diabetes mellitus (T2DM) may increase the chances of unfavorable outcome and delay the recovery from stroke and needs further investigation. **Subjects and Methods:** The study dealt with 208 patients. The neurological status of the patients was assessed by Glasgow Coma Scale and the severity of stroke was assessed by the National Institute of Health Stroke Scale. Patients were divided into two groups: T2DM in group 1 and without T2DM in group 2. We assessed functional improvement by Functional Independence Measure (FIM) Scale, quality of life by Stroke Specific Quality of Life (SSQOL) Scale, and serum levels of brain-derived neurotrophic factor (BDNF) for assessing neuroplasticity. **Results:** We observed lower levels of BDNF in diabetic stroke patients. There was significant improvement in FIM scale scores and SSQOL scale scores in non-diabetic stroke patients after 6 months ($P < 0.05$). The relative risk (RR) of poor functional recovery (FIM) in the diabetic group was 1.34 [95% confidence interval (CI) 1.0–1.8] and the odds ratio (OR) was 1.8 (95% CI 1.03–3.12). Diabetes is an independent risk factor for poor BDNF recovery (serum BDNF < mean value, i.e. 10.07 ± 3.8 ng/mL) (RR 2.40; 95% CI: 1.36–4.21 and OR 1.6; 95% CI: 1.15–2.13] and poor quality of life (RR 1.56; 95% CI: 1.13–2.16 and OR 2.83; 95% CI: 1.14–7.0). **Conclusion:** Diabetes is not only a risk factor for stroke occurrence but also delayed recovery after stroke.

Keywords: Functional recovery, neuroplasticity and quality of life, stroke, type 2 diabetes mellitus

Introduction

Stroke is the major cause of disability. Association of diabetes may increase the chances of unfavorable outcome after stroke. Diabetes is one of the risk factors that can be associated with occurrence, poor outcome, and recurrence of stroke. An increased incidence of stroke had been reported in advanced age in diabetics.[1] Diabetes and ischemic stroke often come up together. Diabetes causes atherosclerotic changes in the heart and the cerebral arteries and is associated with different subtypes of ischemic stroke, including lacunar, large artery occlusive, and thromboembolic strokes.[2] In patients suffering from diabetes, the course of stroke is more severe. In such patients, cerebral edema appears more often and mortality is higher.[3] Energy metabolism and neurotransmission are closely interrelated because glutamate, γ-amino butyric acid (GABA), acetylcholine, and glycine are synthesized through glucose metabolic pathways. The metabolism of glucose generates carbon for biosynthesis of amino acids and sugars. The sugar is further used for synthesis of glycoproteins and glycolipids and for synthesis of tri-carboxylic acid cycle-derived neurotransmitters glutamate and GABA. In diabetes, changes in the metabolic rate of glucose increase production of sorbitol and elevate oxidative stress.[1]

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Recovery of the motor and sensory function is mediated by resolution of edema, unmasking of old neural pathways, neurogenesis, and synaptogenesis. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin's family, which plays a key role in regulating survival, growth, maintenance of neurons, learning, and memory.[4,5] An animal study has shown that a major portion of BDNF is formed and secreted by the hippocampus in the brain. BDNF reduces food intake and lowers blood glucose levels in obese diabetic mice.[6-8] BDNF is also expressed in several non-neuronal tissues, and platelets are the major source of peripheral BDNF.[9] The impact of diabetes on functions of brain is well-known, but its effects on functional recovery, neuroplasticity, and quality of life in stroke patients need further investigation.

Subjects and Methods

A total of 245 patients with first ever stroke were included in this prospective study. Patients who were admitted to the Department of Neurology in our hospital, Lucknow, India, were recruited. The study was approved by the ethical committee of our institute. Out of 245, only 208 patients were available at the end of 6 months for analysis. Patients were divided into two groups: group 1 [type 2 diabetes mellitus (T2DM), $n = 104$] and group 2 (without T2DM, $n = 104$). An approved written informed consent was signed by all subjects prior to inclusion into the study. The criteria followed for inclusion were patients with (1) first ever stroke, (2) between 18 and 70 years of age, and (3) both males and females. Exclusion criteria were (1) recurrent stroke, (2) aphasia, (3) comatose patients, (4) pregnancy, (5) multiple organ failure, (6) psychiatric illness, (7) movement disorder, (8) patients with functional impairment before first stroke, and (9) patients with amputation.

Assessment of serum levels of BDNF

BDNF blood concentration on the first day of admission was estimated. Two milliliters of blood was collected and allowed to stand for 1 h at room temperature. The sample was then centrifuged and the serum was separated by centrifugation of blood sample at 1500*g* and stored at −80°C for further processing.[10] Serum concentration of BDNF was assessed by enzyme linked immunosorbent assay (ELISA) using double-sandwich human BDNF ELISA kit (Raybiomed, Boster). Seven standard concentrations (2000, 1000, 500, 125, 62.5, 31.2, and 0 ng/mL) were assessed for the corresponding OD values and a standard curve was generated. The OD values of samples were read by the ELISA reader at wavelength 450 nm.

Statistical analysis

We used SPSS 20.0 (Statistical Package for the Social Sciences) to analyze the data and plot the charts. The values in our data were normally distributed, so parametric tests were used to analyze the data. Mean, standard deviations, odds ratios (ORs), and relative risks (RRs) were calculated by descriptive statistics. We used independent *t*-test to compare means in between two groups. Chi-square test was used to compare the categorical variables in between groups. Multiple regression was used to assess risk factors for poor outcome after stroke. A P -value of <0.05 was taken significant to draw our conclusion.

Results

The study dealt with 208 patients with stroke. The mean age of the patients in diabetics was 56.29 ± 11.06 years and in non-diabetics was 57.42 ± 10.35 years. In our study, 50% of patients were diabetic. There was no significant difference in male-to-female ratio and side affected in both groups. Ischemic stroke was the most common in diabetics. The ratio of ischemic to hemorrhagic stroke was 2:1 in group 1 and 1:4 in group 2. In the diabetic group, 80% of patients were hypertensive, 42% were smoker, and 29% had dyslipidemia. Patients were diagnosed as hypertensive with blood pressure 150/90 mm Hg or higher at age ≥60 years and older, or 140/90 mm Hg or higher in adults <60 years.[11] Cigarette smoking was defined as having smoked at least one cigarette per day for 1 year or more.[12] Serum total cholesterol <200 mg/dL, low-density lipoprotein (LDL) cholesterol <100 mg/dL, triglyceride <150 mg/dL, and high-density lipoprotein (HDL) >40 mg/dL were taken as normal.[13]

All patients were oriented to time place and person (Glasgow Coma Scale was between 14 and 15). Scores of modified Rankin scale were more impaired in the diabetic group; however, the difference was not significant. There was no significant difference in biochemical findings of lipids (total cholesterol, HDL, LDL, very low-density lipoprotein) in both groups ($P > 0.05$) at the time of admission [Table 1]. No significant difference was found in Functional Independence Measure (FIM) scores on admission ($P > 0.05$) and after 2 weeks ($P > 0.05$), but recovery was better in non-diabetic group after 6 months (FIM scores $P < 0.01$) [Figure 1]. On comparing the quality of life in both groups, we found significant difference in Stroke Specific Quality of Life (SSQOL) scores after 6 months ($P < 0.05$) [Figure 1]. The mean BDNF score at the time of admission in all subjects was 10.07 ± 3.9 ng/mL. In both groups, we found significant difference in BDNF levels on admission ($P < 0.01$). Better rise

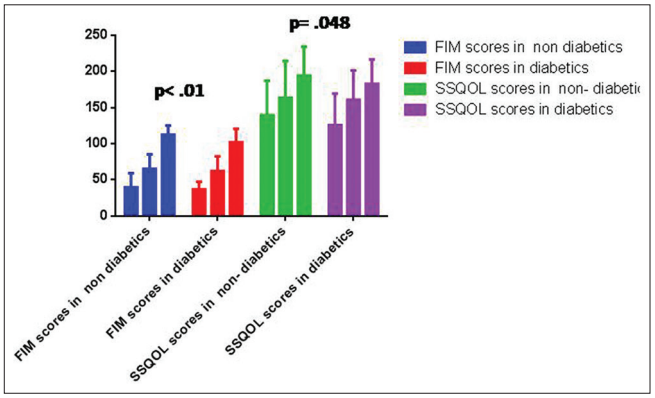

Figure 1: FIM and SSQOL scale scores in subjects with and without diabetes on admission, after 2 weeks, and after 6 months

in BDNF levels was noticed in non-diabetic stroke patients with significant difference after 2 weeks ($P < 0.01$) and after 6 months ($P < 0.01$) [Table 2]. On analysis, we found that diabetes, whether alone or associated with hypertension, is a risk factor for poor neuroplasticity, that is recovery of BDNF levels after stroke [Table 3]. Patients having FIM score >62 and BDNF levels > mean values (10.07 ± 3.8 ng/mL) at the time of admission were taken as improved.[14,15] The RR of poor functional recovery (FIM) in the diabetic group was 1.34 (95% CI 1.0–1.8) and OR was 1.8 (95% CI 1.03–3.12). Diabetes is an independent risk factor for poor BDNF recovery (BDNF levels less than mean, 10.07 ± 3.8 ng/mL) (RR 2.40; 95% CI: 1.36–4.21 and OR 1.6; 95% CI: 1.15–2.13) and poor quality of life (RR 1.56; 95% CI: 1.13–2.16 and OR 2.83; 95% CI: 1.14–7.0).

Discussion

Diabetes is associated with more ischemic strokes. Diabetic patients have up to a three-fold increased risk for suffering a stroke, compared with non-diabetics. Hypertension associated with diabetes is also a cause of hemorrhage into the brain tissue. Diabetes leads to many complications involving the nervous and musculoskeletal system. In diabetics, distal symmetrical sensorimotor polyneuropathy (DPN) is the leading cause of non-traumatic limb amputation. Diabetic autonomic neuropathy (DAN) can affect any body system and is associated with greatly increased morbidity and mortality and can have a profound influence on the quality of life.[16] Patients without diabetes had better improvement in FIM [Figure 1] and SSQOL [Figure 1] scores on admission and at discharge after 2 weeks. However, the differences were significant after 6 months ($P < 0.01$). Similar results were found in a previous study by Mizrahi *et al.* (2007) that there is no difference in the functional outcome of diabetic and non-diabetic patients on admission and discharge.[17] But in our study, patients were followed till 6 months and we observed the differences in outcome after 6 months of stroke. As expected, we found that the incidence rate of hospitalization due to ischemic stroke was higher among those with than those without diabetes in all the years studied.[18] Diabetes is often associated with a number of diseases and medical conditions such as hypertension, obesity, dyslipidemia, hyperglycemia, and inflammation that accelerate and aggravate the atherosclerotic process and thus favor the onset of stroke.[19]

In diabetes mellitus, excessive glucose metabolism generates excess nicotinamide adenine dinucleotide hydrogen (NADH), which induces oxidative stress and damage to mitochondria. A combination of oxidative stress and hyperglycemia activates the detrimental pathways of advanced glycation end products (AGE), polyol, hexosamine, and protein kinase C (PKC) pathways. Diabetes leads to redox imbalance, gene expression disturbances,

Table 1: Sociodemographic factor and baseline values of subjects

Variables	Group 1 (diabetic) *n*=104	Group 2 (non-diabetic) *n*=104	*P*
Age (years)	56.29 (11.06)	57.42 (10.35)	0.79[a]
Sex (female/male) (*n*)	48/56	40/64	>0.05[a]
Side affected (left/right) (*n*)	39/65	52/52	>0.05[a]
Type (ischemic/hemorrhagic) (*n*)	74/30	23/81	**<0.042a***
Hypertensive (%)	80	70	0.89[a]
Dyslipidemia (%)	29	17	**0.04a***
Smoking (%)	42	33	0.32[a]
GCS (SD)	14.76 (0.21)	14.88 (0.41)	0.827[b]
NIHSS (SD)	9.36 (4.17)	8.01 (4.14)	0.921[b]
ICH score (range)	2 (1-3)	1.5 (0-3)	0.612[b]
mRS (SD)	3.66 (0.895)	3.45 (0.75)	0.820[b]
Length of hospital stay (days)	22 (4.18)	11 (2.3)	**0.03b***
Cholesterol	178.47 (47.76)	167.00 (55.74)	0.434[b]
Triglyceride	157.00 (55.74)	178.47 (47.76)	0.434[b]
HDL	46.78 (13.45)	40.38 (9.43)	0.280[b]
LDL	96.75 (40.97)	112.95 (43.05)	0.400[b]
VLDL	16.50 (8.38)	19.00 (13.04)	0.616[b]

GCS: Glasgow Coma Scale, NIHSS: National Institute of Health Stroke Scale, mRS: Modified Rankin Scale, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, SD: Standard deviation. *Significance level <0.05. Bold value *P*=0.042

Table 2: Serum BDNF levels in stroke patients with and without type 2 diabetes mellitus

Parameter	Group 2 *n*=104 Mean±SD	Group 1 *n*=104 Mean±SD	*P*	95% CI	
				Lower	Upper
S. BDNF level (ng/mL)					
On admission	11.08±3.85	8.77±4.04	0.001**	−3.79	−1.17
After 2 weeks	12.68±4.21	9.43±1.98	0.002**	−4.51	−2.21
After 6 months	15.38±3.44	10.90±2.05	0.001**	−7.03	−3.39

CI: Confidence interval, SD: Standard deviation, BDNF: Brain-derived neurotrophic factor. *Significance level <0.05, **significance level <0.01

and further oxidative stress. These pathways also induce inflammation and neuronal dysfunction.[8] Diabetes also leads to early degenerative changes in musculoskeletal system, and hence many musculoskeletal manifestations such as peri-arthritis of shoulder joint, limited joint mobility, back pain due to formation of osteophytes, radiculopathy, reflex sympathetic dystrophy, Dupuytren's contracture, muscle atrophy, generalized body pain, flexor tenosynovitis, joint destruction, and diabetic amyotrophy. All these manifestations may or may not affect functional activities but negatively affect the quality of life.[20] In a study by Huynh *et al.* (2017), diabetes impairs the capacity for neuroplasticity such that patients experience a slower and poorer recovery after stroke. Transcranial magnetic stimulation was used to assess cortical function and threshold-tracking in 57 participants, and absence of ipsi-lesional cortical excitability change after diabetic strokes was found, suggesting impaired capacity for neuroplasticity over this hemisphere as a consequence of a "double-hit" phenomenon because of pre-existing alterations in cortical function in non-stroke patients with diabetes over the ipsi-lateral and contra-lesional hemispheres.[21]

Low BDNF concentrations have been observed in patients with metabolic syndrome,[22] atrial fibrillation,[23] and acute coronary syndromes.[24] We also observed lower levels of BDNF in stroke patients with T2DM [Table 2]. Diabetes is an independent risk factor for stroke. Secretion of neurotrophic factors by the cerebral endothelium, such as BDNF, is suppressed in diabetes [Figure 2]. Consequently, this neuroprotective deficit makes neurons more vulnerable to injury.[25] Diabetes mellitus significantly elevates the risk for a variety of neurologic diseases, including stroke.[26-29] Age-adjusted incidence rates suggest that diabetic patients are three times more likely to have a stroke compared with non-diabetic patients, a disparity that is seen across multiple racial/geographic groups.[30-32] In addition, diabetes is associated with more severe strokes, in-hospital mortality, and slower recovery compared with non-diabetic individuals.[33-36] Diminished cognitive abilities are found in patients with type 1 diabetes, whereas type 2 diabetes is known to also affect learning and memory.[37,38] Many population-based studies have found an association between diabetes and an increased risk of developing Alzheimer's disease and vascular dementia.[39,40] Diabetes is one of the vital comorbidity risk factors reported to be associated with occurrence, poor outcome, and recurrence of stroke in patients.[41-43] An increased incidence of stroke has been reported in advanced age among diabetic patients.[44] A previous study has indicated better improvement in functional activities in non-diabetic patients when compared with diabetic stroke patients. This indicates that neuroplasticity becomes slow in diabetics.[45]

We also observed that patients with diabetes had other complications such as pneumonia, urinary tract infection, and recurrence of infection. According to Liao *et al.* (2015), the incidences of stroke in cohorts with and without diabetes were 10.1 and 4.5 per 1000 person/years, respectively.[46] During the follow-up period, diabetic patients had an increased risk of stroke (adjusted hazard ratio: 1.75; 95% CI: 1.64–1.86) than those without diabetes. Associations between diabetes and stroke risk were significant in both sexes and all age groups. Previous diabetes was associated with post-stroke mortality (OR: 1.33; 95% CI: 1.19–1.49), pneumonia (OR: 1.30; 95% CI: 1.20–1.42), and urinary

Table 3: Risk factors for poor improvement in BDNF levels and FIM scores 6 months after stroke

Parameters	S. BDNF levels		FIM scores	
	t	*P*	*t*	*P*
Both T2DM + HTN	4.27	0.001**	3.178	**0.002****
HTN	−2.31	0.024	0.667	0.506
T2DM	3.53	0.01**	3.02	**0.049***

HTN: Hypertension, T2DM: Type 2 diabetes mellitus, FIM: Functional Independence Measure, S. BDNF: Serum brain-derived neurotrophic factor. *Significance level <0.05, **significance level <0.01

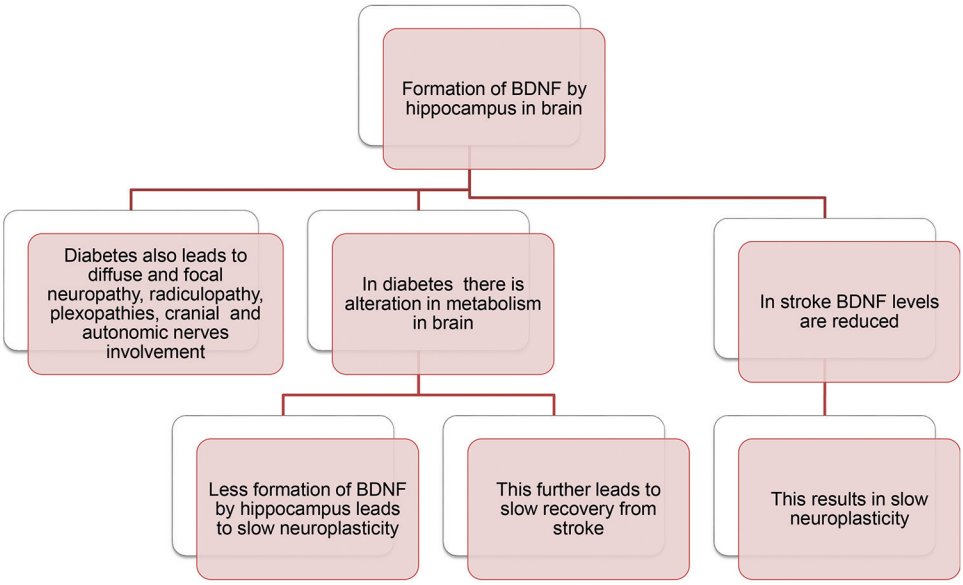

Figure 2: Possible causes of reduced BDNF levels in diabetes

tract infection (OR: 1.66; 95% CI: 1.55–1.77). The impact of diabetes on adverse events after stroke was investigated particularly in those with diabetes-related complications.[46] BDNF also has correlation with pain. Lee *et al.* (2014) have assessed the effects of yoga on serum levels of BDNF and low back pain and found that BDNF levels were raised and pain reduced after 12 weeks of yoga. They concluded that BDNF may be one of the key factors mediating beneficial effects of yoga on chronic low back pain.[47]

The quality of life after stroke not only depends on improvement of functional activities but also on vision. Impairment of vision may reduce the quality of life. In our study, patients with poorly controlled blood sugar levels and chronic diabetics also had complains of visual disturbances, but we did not mention the assessment protocols and the details of findings in this article. Stroke itself is the cause of decline in quality of life, but comorbidities associated with stroke may also contribute to the negative outcome or slow recovery. Slow recovery or prolonged disability increases the burden on patients and care givers. This may result in irritable mood, aggressive behavior, and depression. In our study, we observed that patients with slow recovery had irritable mood, loss of interest in social activities, aggressive behavior, decline in work productivity, and loss of appetite. Low levels of BDNF may be the cause of depression or depression may further decrease the BDNF levels.[48] It is very important that every patient should be assessed for depression and adequate management should be done so as to reduce the chances of delay in stroke recovery and decline in quality of life after stroke.

Studies suggest that BDNF also has a role in glucose metabolism.[49,50] Early rehabilitation should be implemented in stroke patients to promote better neuroplasticity. Exercise has beneficial effects on glucose levels in diabetics. One cause of this effect may be the rise in BDNF levels after exercise. Proprioceptive neuromuscular facilitation (PNF) is the standardized and the choice of rehabilitation protocol in our department and it has beneficial effects on functional outcome, gait, and balance in acute and chronic stroke patients.[51,52] Despite the beneficial effects of PNF exercises in all patients, diabetic patients exhibited less improvement in FIM scores when compared with the non-diabetics after 6 months; however, the difference was not significant after 2 weeks.

BDNF also has association with the immunity and inflammation. Lower levels of BDNF result in not only poor functional outcome but also inflammation and poor immunity.[53,54] Patients with lower levels of BDNF may also have chances of recurrent stroke. Assessment of BDNF in acute stage of stroke and detection of lower levels can help in preventing the recurrent stroke, recurrent infection such as urinary tract infection, respiratory tract infection, and further mortality.

Conclusion

We observed slow rise in BDNF levels in T2DM when compared with the stroke patients without T2DM. Lower levels of BDNF were also associated with slow recovery in functional activities and quality of life. The study reveals that T2DM impedes functional recovery, quality of life, and neuroplasticity after stroke.

Limitations of study

We did not measure HbA1C in diabetic stroke patients during admission and after 6 months.

Recommendations and implications for future research

We found positive association between levels of BDNF with functional recovery, quality of life, and neuroplasticity. So, raising the level of BDNF by means of intensive rehabilitation or direct application of BDNF to the patients with stroke can improve the functional outcome. Intravenous application of BDNF has been tried in animals with positive findings. In humans, the studies are still lacking. In future, this study can help in better management of patients with stroke.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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