Guidelines for Stroke Survivors With Diabetes Mellitus

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In the United States, diabetes mellitus is the seventh leading cause of death, and 65% of these deaths are attributable to cardiovascular disease or stroke or to both.[1,2] Moreover, diabetes mellitus is an established and independent risk factor for stroke and is associated with a 1.8- to ≈6-fold increased risk compared with nondiabetic subjects.[2,3] Currently, 12.2% (30.3 million) US adults over the age of 18 years has diabetes mellitus with 23.8% (7.2 million) unaware they have diabetes mellitus.[1] Prediabetes, a precursor to type 2 diabetes mellitus, is estimated to occur in 33.9% (84.1 million) US adults.[1] Moreover, a meta-analysis of 102 prospective studies reported that persons with diabetes mellitus had a 2.3× higher risk of developing ischemic stroke and a 1.6× higher risk of developing hemorrhagic stroke compared with nondiabetics.[4] Among patients admitted for acute stroke, diabetes mellitus was associated with a higher risk of death, functional dependency, and stroke recurrence.[5,6]

Hyperglycemia is a common problem in persons with diabetes mellitus after an acute stroke.[5,6] Elevations in serum glucose can be because of many factors, such as age, obesity, and physiological stress. Maintaining therapeutic blood glucose levels postacute stroke can present extreme challenges. Therefore, reasonably tight, yet therapeutic, control of hyperglycemia in persons with diabetes mellitus after a stroke must be a priority. The purpose of this article is to describe (1) major evidence-based interventions to maintain normal glucose levels and improve outcomes in persons with diabetes mellitus after an acute stroke, and (2) the critical role nurses play in the prevention and control of hyperglycemia in persons with diabetes mellitus after a stroke.

Pathophysiology

Several mechanisms associated with diabetes mellitus lead to stroke. Persons with diabetes mellitus have stiffer arteries, early structural changes, and decreased elasticity compared with individuals without diabetes mellitus.[7] The physiological stress of a stroke contributes to increased circulating counter regulatory hormones (cortisol, catecholamine's, growth hormone, glucagon) and proinflammatory cytokines.[7] These combined factors lead to excessive glucose production and reduced glucose uptake.[7] Hyperglycemia has also been shown to worsen acute ischemic brain injury (increase brain edema, brain herniation, infarct size, and decrease reperfusion) that potentially increase the risk of morbidity and mortality in persons with diabetes mellitus.[5–7] Higher glucose levels on admission in persons with and without diabetes mellitus have been associated with increased mortality, worse poststroke outcomes, and stroke recurrence.[8] It has been further reported that ≈20% to 35% of hospitalized patients have a history of diabetes mellitus, and another 58% without a history of diabetes mellitus on admission have a plasma glucose >110 mg/dL.[9] Thus, maintaining glucose levels within normal ranges are important for long-term survival poststroke in persons with diabetes mellitus.

Evidence-Based Guideline for Glucose Management During and Poststroke

The American Heart Association/American Stroke Association[10] and the American Diabetes Association[11] have provided guidelines for the early management of patients with acute ischemic stroke recommending serum glucose concentrations in the range of 140 to 180 mg/dL (7.8–10 mmol/L) during the first 24 hours in all hospitalized patients. Typically, hyperglycemia in the acute stroke setting is treated with subcutaneous insulin through a sliding scale. Normalization of blood glucose during the first 48 hours of hospitalization has survival benefits in patients experiencing ischemic stroke.[12] The National Institute of Neurological Disorders and Stroke–funded THIS (Treatment of Hyperglycemia in Ischemic Stroke)[12] and the GRASP (Glucose Regulation in Acute Stroke Patients)[13] trials both demonstrated safety and feasibility of insulin infusion therapy for intensive glucose control in patients with acute ischemic stroke. However, a recent systematic review of 11 randomized controlled trials involving 1583 participants determined that intensive glucose control (72–135 mg/dL) using insulin, immediately after acute ischemic stroke, found no differences between intensive or convention glucose control on dependency, neurological deficit, or mortality at 30 or 90 days.[14] Similar results were found in a subgroup analysis between persons with or without diabetes mellitus; however, increase in severe hypoglycemia was reported. The authors concluded no evidence supported the use of intensive insulin therapy for tight glucose control after acute stroke in persons with or without diabetes mellitus.[14] Yet, the GLIAS-II (Glycemia in Acute Stroke II) study demonstrated that glucose levels ≥155 mg/dL were associated with poorer outcomes poststroke.[15] As a result, the Society of Hospital Medicine provides a free comprehensive

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resource manual that includes evidence-based guidelines to assist nurses in developing strategies and protocols to monitor glucose levels in the hospital setting.[16] Their manual contains multiple examples of insulin administration protocols, resources, and suggestions that can be adapted according to the needs of the institution on developing and implementing intensive glucose management protocols (eg, personnel, time, training, charting, and tracking capability, etc).[16]

The SHINE trial (Stroke Hyperglycemia Insulin Network Effort), a multicenter randomized controlled trial of 1400 patients, is currently being analyzed to assess the targeted glucose concentration (80–130 mg/dL) that would be safe and result in improved 3-month poststroke outcome.[17] This study will provide valuable evidence about the optimal management of hyperglycemia, as well as the development of a standard protocol that describes the optimal level of glucose in acute stroke as well as its efficacy and safety. In addition, the SHINE study will produce data on the frequency of glucose monitoring needed to avoid the onset of both hyperglycemia and hypoglycemia.

Glycemic Targets and Recommendations

The benefits of glycemic control on morbidity reduction through implementation of intravenous insulin protocols administered using evidence-based practice algorithms are well described in the literature.[16–21] The nurse plays a pivotal role in consistently monitoring and safety managing glucose levels in both the short- and long-term care of patients during and after stroke.[22–25] In clinical practice, the first step is to document glucose levels on admission and in the poststroke state to evaluate its severity and duration. It is recommended that insulin therapy be initiated for treatment of persistent hyperglycemia starting at a threshold 180 mg/dL.[10,11] Once insulin therapy is started, a target glucose range of 140 to 180 mg/dL is recommended for the majority of critically ill patients, including those with diabetes mellitus. A meta-analysis of >26 studies, including the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study, revealed increased rates of severe hypoglycemia (blood glucose <40 mg/dL) and mortality in tightly versus moderately controlled cohorts.[25] In the GLIAS-II study, it was demonstrated that lack of response to conventional glucose management (<155 mg/dL) within the first 48 hours was associated with poor outcomes poststroke.[15] Nurses should perform ongoing assessments to evaluate the response to glucose management, including changes in the trajectory of glucose levels, intake and output, nutritional status, illness/infection, renal function, and neurological function (cognitive status). Early documentation and immediate correction of these abnormalities are important to long-term outcomes of patients poststroke, including those with diabetes mellitus.

Nursing Implications

An essential responsibility of the nurse is to manage hyperglycemia during and poststroke, as well as understand the pathophysiology of hyperglycemia and how its effective control prevents devastating long-term morbidity and mortality.[16,22–25] Guidelines have been provided by the American Heart Association/American Stroke Association, American Diabetes Association, and the Society of Hospital Medicine.[10,11,16] Because of their continued interactions with patients, nurses frequently serve as an essential bridge of care between the patient, their providers, and their families. Investing in initial and continuing diabetes education will pay significant dividends in the long-term outcomes of persons with diabetes mellitus poststroke. Given the large number of nurses at most institutions, a multifaceted approach, such as 1:1 encounters, web-based modules, including educational modules of primary care and self-management content (eg, insulin protocols, case studies), are suggested strategies. Unit-based meetings and annual data review should be a regular component of nursing/provider in-services, grand rounds, and continuing education programs to keep all parties engaged in patient care and updated protocols.[26] Once patients are stabilized, it is important for the nurse to create an individualized diabetes management plan (ie, lifestyle recommendations; changes in physical activity [walking 10 000 steps/d if tolerated]: dietary recommendation [low carbohydrate diet, low sodium and cholesterol, increase in fresh fruits and vegetables] and medications), as well as poststroke care with the patient and their families.[11,27] Table I in the online-only Data Supplement is a synthesis of the current literature reflecting lifestyle management poststroke in persons with diabetes mellitus. Nurses and discharge planners should also assist the patient and caregivers identify appropriate resources, such as the American Association of Diabetes Educators, American Diabetes Association, American Stroke Association, Life after a stroke, StrokeAide.com, or other rehabilitation services located within the community for continued support and management.

Conclusions

The danger of poststroke hyperglycemia is well established in persons with and without diabetes mellitus. Data confirm a strong association between hyperglycemia and poor outcomes, in persons with diabetes mellitus as well as those with high admission glucose levels. Table II in the online-only Data Supplement provides a summary of the literature of evidence-based guidelines of glucose levels poststroke. Although there is compelling evidence that hyperglycemia has an effect on stroke outcome, debate continues as to whether the effect is independent of the influence of diabetes mellitus or initial stroke severity. The pathogenesis of hyperglycemia and the pathophysiology that underlie detrimental effects of hyperglycemia remain unclear. A distinction between unknown diabetes mellitus and nondiabetic hyperglycemia seems important because prognosis and effect of intervention have been shown to differ in these 2 groups. The documentation of glucose on admission is essential. When treating hyperglycemia, the nurse should be cautious in the correction of glucose to avoid hypoglycemia, all of which can be detrimental to the brain and affect future patient outcomes. Careful use of insulin infusion protocols seems advisable when accompanied with frequent glucose monitoring and documentation, especially during the first 48 hours poststroke. Rigorous studies, such as the SHINE study, are needed to assess the value of insulin therapy and to determine the optimal blood glucose targets in patients with diabetes mellitus poststroke.[17] Nurses continue to be

an essential team member in monitoring and documenting glucose levels, patient outcomes, and education to patient, family, and providers.

TAKE-HOME POINTS

- Nurses play a pivotal role in accurate documentation and treatment of hyperglycemia in persons with diabetes mellitus poststroke.
- Management of hyperglycemia requires the use of evidence-based protocols that include glucose levels, initiation of intravenous insulin, instructions for sliding scale insulin, and when to stop insulin and begin subcutaneous insulin administration.
- Nurses should be involved with the education of the person with diabetes mellitus and their families to prevent future stroke and diabetes mellitus management, as well as rehabilitation resources when needed.

Disclosures

None.

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SUPPLEMENTAL MATERIALS

Table I: Lifestyle recommendations for individuals with diabetes post stroke.

Physical activity and Exercise Program

- According to limitations and recommendations by primary care provider and cardiologist
- Comprehensive evaluation
- Rehabilitation program and physical therapy recommended
- Exercise prescription should be safe and based on limitations
- Based on:
  - Frequency
  - Intensity
  - Time
  - Type
- Includes a progressive combination of the following:
  - Cardiovascular
  - Resistive
  - Flexibility

Diet Recommendations

- Low carbohydrate diet, increase in complexed carbohydrate and less simple carbohydrate
- Increase of fresh fruits and vegetable
- Low sodium
- Low cholesterol foods
- Less trans fat
- Decrease in fried foods

Medications

- Follow-up primary care provider for medication changes and/or alteration

Secondary Risk factor Modification

- Cholesterol-lowering medications
- Antihypertensive medications
- Aspirin (lowers secondary stroke risk by 80%)
- Frequent follow-up with primary care provider and health care team

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Table II: Summary providing evidence based guidelines of glucose levels post stroke

Author (reference#)	Type of study	Purpose	Number of subjects	Follow-up post stroke (hours)	Glucose range	Results
Bellolio (1)	Systematic Review of Randomized controlled trials (RCTs)	To determine whether intensively monitoring insulin therapy aimed at maintaining serum glucose within a specific normal range (70 to 135 mg/L) in the first 24 hours of acute ischemic stroke influences outcome.	11 RCTs involving 1583 participants n=791 intervention group n=792 control group	24 hours	70 to 135 mg/L (4-7.5 mmol/L	No difference between the intervention and control groups in the outcomes of death, dependency or final neurological deficit. In subgroup analyses of diabetes mellitus (DM) versus non-DM, there was no difference for the outcomes of death, disability or neurological deficit.
Bruno (2)	Randomized multicenter, blinded pilot trial	To test the feasibility and tolerability of aggressive hyperglycemia correction with intravenous insulin compared with usual care during acute cerebral infarction.	Total N= 46 n=31 aggressive intervention n=15 usual care	cerebral infarction within 12 hours after onset	aggressive-treatment group <130 mg/dL (7.2 mmol/L) usual-care group <200 mg/Dl (<11.1mmol/ L	The intravenous insulin protocol corrected hyperglycemia during acute cerebral infarction significantly better than usual care without major adverse events.
Bruno (3)	Randomized, blinded, multicenter, phase III trial	To determine the safety and efficacy of standard vs. intensive glucose control with	1400 subjects randomly assigned to	12 h of stroke symptom onset. Administration	-sliding scale SQ insulin (blood glucose	The primary outcome is a baseline severity adjusted 90-day modified Rankin

		insulin in hyperglycemic acute ischemic stroke patients.	-sliding scale subcutaneous (SQ) insulin or -continuous intravenous insulin	of insulin to control glucose levels for up to 72 h	range 80-179 mg/dL (4.4 -9.9 mmol/L) continuous intravenous insulin (target blood glucose 80-130 mg/Dl (4.4 -7.2 mmol/L)_	Scale score and the rate of severe hypoglycemia. This trial will provide important novel information about preferred management of acute ischemic stroke patients with hyperglycemia. It will determine the potential benefits and risks of intensive glucose control during acute stroke.
Gray (4)	Multicenter RCT with blinded outcome assessments	To determine whether treatment with glucose-potassium-insulin (GKI) infusions to maintain euglycaemia immediately after the acute event reduces death at 90 days or severe disability at 90 days.	Intervention: n=354 received GKI protocol Control: n=400 received saline, no glucose control	within 24 hours of stroke onset	70 - 130 mg/Dl	There was no significant reduction in mortality or severe disability at 90 days (GKI vs. control). The overall mean plasma glucose and mean systolic blood pressure were significantly lower in GSK vs. control group
Finfer (5)	Randomized Control clinical trial	To test the hypothesis that intensive glucose control reduces mortality at 90 days.	n=3054 intensive control n=3050 conventional control	Within 24 hours after admission to an intensive care unit (ICU)	intensive control, glucose-81 to 108 mg/dL (4.5 to 6.0 mmol/L), Convention	Intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.

					control glucose- 180 mg/dL or less (10.0 mmol /L or less per liter).	
Fuentes (6)	Multicenter, prospective, observational academic cohort study	To analyze the effect of conventional glucose management, which aimed to maintain glucose levels <155 mg/ dL (8.5 mmol/L), on glucose control and the outcomes of patients with acute ischemic stroke (IS) in a clinical practice setting.	Total n = 213 -(n=113) Untreated with persistent glucose <155 mg/dl -(n=11) Treated and good responders with persistent glucose levels <155 mg/dl -(n=58) Treated and non-responders (glucose levels ≥ 155 mg/dl after treatment) -(n=31) Untreated and glucose levels	acute IS <24 hours	120 and 155 mg/dL (6.6–8.5 mmol/L).	Lack of response to conventional treatment to maintain capillary glucose levels under 155 mg/dL (8.5 mmol/L) within the first 48 hours is associated with poor outcomes in patients with acute ischemic stroke.

			≥155 mg/dl within the first 48 hours			
Johnston (7)	Prospective RCT	To compare difference between IV and SQ insulin infusion vs continuous IV insulin infusion is patients with ischemic stroke less than 24 hours	Tight control n=24 glucose 70-110 mg/Dl IV insulin infusion and meal SQ injections Loose control n=25 glucose 70-200 mg/dL IV insulin infusion and meal SQ injections Usual care n=25 glucose 70-300 mg/Dl Only used insulin if glucose rose above 300mg/dL	<24 hours	Tight control IV and SQ insulin (glucose-70-110 mg/dL (3.9- 6.1 mmol/L), Loose control glucose 70-200 mg/dL (3.9-11.1 mmol/L) Usual Care 70-300 mg/dL (3.9-16.6 mmol/L)	Insulin infusion for patients with acute ischemic stroke is feasible and safe.

Kreisel (8)	RCT Intervention	To test the safety and feasibility of an IV insulin-only infusion protocol delivered via a pump and SQ insulin in the management of glucose post stroke.	Intervention n-20 IV insulin via pump glucose (80-110mg/dl) Control n=20 SQ insulin injection glucose above 200 mg/dl (11.1 mmol/l	<24 h	Intervention IV insulin infusion Glucose-80-110 mg/dL 4.44-6.11 mmol/l Control SQ insulin injections glucose above 200 mg/dl (11.1 mmol/l	Intensive IV insulin infusion protocol effectively lowers blood glucose levels with an increased risk of manageable hypoglycaemic events. However, an increase in staff is required.
Laird (9)	Systematic review	Systematic review of descriptive cohort studies on the dynamics of glycaemia among adults admitted to hospital with acute stroke.	7 prospective cohort studies and 1 retrospective study	glycemic status monitored over at least 2 consecutive days from admission to hospital	Not reported	IV insulin therapy significantly lowers glucose levels when compared with controls but adherence to glucose monitoring and treatment protocols appeared to pose considerable challenge on nurses in routine stroke care.

Michell (10)	Retrospective cohort study	To evaluate the extent to which hyperglycemia was monitored and managed among patients admitted to hospital with acute stroke and transient ischemic attack.	Total n=112 n=71 Glucose <140mg/dL (<7.8 mmol/L) n=41 Glucose ≥ 140mg/dL (≥7.8 mmol/l)	First 5 days of admission	During first 5 days of admission without DM glucose range 43.2 -433.8 mg/dL (2.4-24.1 mmol/L) With DM 86.4-329.4 mg/dL (4.8-18.3 mmol/L)	Hyperglycemia in the acute stroke phase is likely to persist and, whilst an established diagnosis for diabetes mellitus prompts near patient glucose monitoring, glycemic status more generally is under-monitored, undertreated and under-reported to general practitioners.
Middleton (11)	Nursing Review Article	To highlight nursing's essential contribution to the expedient delivery of acute stroke care by providing evidence-based recommendations for clinical practice processes of care and models of care where nurses have a pivotal role during the first 72 hours from arrival at the emergency	NA	72 hours post admission	NA	Nurses play a crucial role in stroke care and they are well placed to take a leadership role in implementing evidence-based care within the multidisciplinary stroke team

		department through to stroke unit.				
Osei (12)	Retrospective Multicenter, RCT	To assess the association of increased admission serum glucose and impaired fasting glucose with unfavorable outcome after endovascular treatment of acute ischemic stroke.	Total n=514 n=160 with occlusion in posterior circulation n=354 occlusion in anterior circulation	Day 1-7 of admission	Median glucose on admission (n=335) was 122.4 mg/dL (6.8 mmol/L) 26% of patients had elevated glucose levels on admission	Hyperglycemia on admission and impaired fasting glucose in the first week after stoke onset are associated with unfavorable short-term outcome after acute ischemic stroke.
Sarwar (13)	Meta-analysis	To quantify the associations of diabetes mellitus and fasting glucose concentration with risk of coronary heart disease and major stroke subtypes in people without initial vascular disease.	102 prospective studies n=698,782 no history of heart disease n=410,299 self-report history of diabetes but no fasting glucose to confirm n=195,390 both self-reported diabetes and	NA	Glucose ranges <70 to >180mg/d/L (<4.0 - >10 mmol/L)	Diabetes confers about a two-fold excess risk for a wide range of vascular diseases, independently from other conventional risk factors. In people without diabetes, fasting blood glucose concentration is modestly and non-linearly associated with risk of vascular disease.

			fasting blood glucose n=93,093 information on fasting glucose, but not self-reported diabetes			

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