

Diabetes in stroke: An overview

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Stroke is the second most common cause of death in people with diabetes and can have life-changing effects in survivors. Despite this, it is often underappreciated compared with the more common cause of death, ischaemic heart disease. This article is a review of stroke and its management in people with diabetes, with details on presentation, the effects and management of hyperglycaemia, and the stroke-mimicking effects of hypoglycaemia.

Stroke is a commonly encountered disease; however, there are many ways in which the risk can be reduced. Each year in England, approximately 150 000 people suffer a stroke, whether it is an initial event or a recurrence (Bhatnagar et al, 2015). Stroke is a leading cause of mortality and represents approximately 11% of all deaths within England and Wales (Mant et al, 2004). Most people survive their first stroke but can be left with severely debilitating disease, dependent on others to help with activities of daily living. However, with sufficient management of diabetes and, more importantly, hypertension, the risk of stroke can be reduced.

According to Albers et al (2002), a stroke is defined as an episode of neurological dysfunction with evidence of acute infarction, marked by either persistent clinical signs or characteristic imaging abnormalities. There are two types of stroke, with the majority (85%) being ischaemic in origin and the remainder (15%) being haemorrhagic (Andersen et al, 2009). Haemorrhagic strokes have a number of causes, including hypertension and vascular malformations (i.e. aneurysms or arteriovenous malformation). Ischaemic strokes occur when there is an occlusion in an artery supplying the brain, and they can be either

thrombotic or embolic in aetiology.

The Face, Arm, Speech, Time (FAST) test can be used as a screening tool for stroke outside of hospital in the case of new, sudden-onset symptoms. It is a common and simple tool, as hemiplegia and speech and language difficulties can be easily detected by a member of the public. However, there are many other functions controlled by the brain that are not limited to movement and speech. Other functions include higher cognition, processing, calculating, vision, understanding, pattern recognition, sensory detection, swallowing and many more. Therefore, although the FAST tool is useful for screening, it is fairly limited in its ability to detect the full extent of brain injury.

Most people who have had a stroke are likely to be taking one or more of the following medicines: an antiplatelet agent (e.g. clopidogrel or aspirin), a statin (used to lower blood cholesterol levels), antihypertensive medications, diabetes medications and possibly a blood thinner (e.g. warfarin or a novel oral anticoagulant).

Stroke presentation in diabetes

Diabetes is a major risk factor for stroke. People with diabetes are twice as likely to have a stroke

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Article points

1. Diabetes is a known risk factor for stroke; however, while optimal management of hypertension can mitigate stroke risk, there is little evidence that good long-term glycaemic control has much of an effect.
2. Acute stroke causes metabolic derangements leading to a hyperglycaemic state.
3. Hyperglycaemia in acute stroke expedites evolution of the infarct and can impair effectiveness of thrombolysis when treating ischaemic stroke.
4. Hypoglycaemia may often produce symptoms that mimic those of a stroke.

Key words

- Diabetes
- Haemorrhagic stroke
- Ischaemic stroke
- Thrombolysis

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Box 1. Case study of an acute stroke following previous “silent strokes” in a person with diabetes.

Mr H woke up one morning with the right side of his body paralysed and numb, a right-sided facial droop, inability to speak and double vision. He was brought into hospital and reviewed by the Accident and Emergency doctor, who diagnosed a stroke. He underwent a computed tomography head scan, which showed an acute, left-sided parietal–temporal infarct and multiple mature lacunes scattered throughout. He had never previously experienced any such symptoms, and had never been diagnosed with stroke despite mature radiological findings suggesting such a history. It was thought that he had likely undergone an acute stroke this episode but had suffered silent strokes in the past.

Page points

1. Stroke is the second most common cause of death in people with diabetes after ischaemic heart disease.
2. Hypertension is the most important risk factor for stroke and should be well controlled in people with diabetes; however, there is no evidence that good long-term glycaemic control can improve stroke risk.
3. People with diabetes often have “silent strokes” that go undiagnosed; they thus have fewer warning signs than people without diabetes and are more likely to present with a large stroke rather than a transient ischaemic attack.
4. Elevated blood glucose levels are common in the acute stroke setting.

compared to those without the condition. The risk increases with the duration of time that a person has had diabetes, by around 3% per year on average (Air and Kissela, 2007). The increased risk can be attributed to the acceleration of the atherosclerotic process as a result of hyperglycaemia. A chronically raised serum glucose level causes endothelial dysfunction, which in turn promotes processes that lead to atherosclerotic plaque formation and rupture (Seidu et al, 2016).

Stroke is the second most common cause of death among people with diabetes; however, it may have been underappreciated in the past owing to the high incidence of cardiac-related mortality (Tuomilehto et al, 1996). While the most significant cause of death in people with diabetes is ischaemic heart disease, which accounts for approximately 50% of deaths, it is known that around 20% die as a result of stroke.

Diabetes is an independent risk factor not only for stroke but also for hypertension (Harris et al, 1995). Hypertension is regarded as the most important risk factor for stroke; therefore, it is of paramount importance that blood pressure is also checked and kept well controlled in people with diabetes. Good hypertensive management has been shown in a number of randomised control trials to reduce the incidence of stroke in the diabetes population (Seidu et al, 2016).

In contrast to high blood pressure, surprisingly, there is at present no evidence to suggest that good long-term glycaemic control reduces the incidence of stroke or improves survival following acute stroke (Air et al, 2007). The evidence does, however, support identifying and treating other risk factors for stroke in people with

diabetes, namely hypertension, smoking, and hypercholesterolaemia (Seidu et al, 2016).

It is well known that people with diabetes are more prone to “silent” myocardial infarction (MI) than the general population. This is when the individual has an asymptomatic MI which is only discovered in retrospect, often incidentally. A similar phenomenon is known as a “silent stroke”, in which the person has a stroke or transient ischaemic attack (TIA) with minimal or no symptoms. It has been shown in some studies that diabetes is an important risk factor for having a silent cerebral infarction (Eguchi et al, 2003). The pathogenesis of these silent events is thought to be related to diabetic neuropathy impairing the person’s perception of the insult in question.

TIA’s and minor strokes can be regarded as a useful “warning” to both the patient and the medical practitioner that an individual is at high risk of having a stroke, and subsequent preventative measures should be taken. Silent strokes give no such warning; thus people with diabetes are more likely to initially present to medical services with a large stroke rather than a TIA. The case study in *Box 1* illustrates the incidental findings of a silent stroke in a person with diabetes.

Hyperglycaemia and its management in acute stroke

Elevated blood glucose levels are common in the acute stroke setting. On admission, a blood glucose level >6.0 mmol/L is observed in two thirds of all ischaemic strokes, including in people without diabetes (Scott et al, 1999). Hyperglycaemia occurs as a by-product of the stress response produced when a body undergoes a traumatic event such as a stroke. This stress response, which is predominantly mediated by cortisol and noradrenaline release, can cause reactive hyperglycaemia even in people without diabetes. Furthermore, the majority of stroke patients will already have a degree of relative insulin resistance with underlying increased lipolysis. The fragile ischaemic brain tissue is then also damaged by the consequences of anaerobic metabolism through lactic acidosis, free radical production and hyperglycaemia, which leads to peroxidation of the lipid cell membrane and cell lysis. Hyperglycaemia then worsens acidosis within the brain cortex

and aggravates mitochondrial dysfunction in the ischaemic penumbra (Anderson et al, 1999), as well as diminishing vascular reactivity to the region (Kawai et al, 1997). Therefore, the issue of hyperglycaemia extends to not only the initial stroke area but also the penumbra, and poor glycaemic control can expedite evolution of the infarct. Hyperglycaemia has been proven to augment changes in the infarct volume (Baird et al, 2003).

A systematic overview of 33 studies highlighted the importance of controlling hyperglycaemia, given the negative effects of high blood glucose on clinical outcomes (Capes et al, 2001). However, a 2014 Cochrane review showed that maintaining serum glucose within a specific range during the acute phase of stroke using intravenous insulin did not provide benefit in terms of morbidity or mortality; it did, however, increase the risk of hypoglycaemia (Bellolio et al, 2014).

In addition to its direct effects on brain tissue, hyperglycaemia also affects potential treatments. Thrombolysis, which is a potentially hazardous treatment used to dissolve clots in certain cases of ischaemic stroke, has been associated with an increased rate of haemorrhagic events in hyperglycaemic patients (Lindsberg and Kaste, 2003). Additionally, thrombolytic therapy has been shown to have reduced efficacy at recanalisation of the blood vessels when used in a hyperglycaemic state (Ribo et al, 2005). This then affects the clinical decision of whether or not to use thrombolysis in acute ischaemic stroke, as the risk–benefit ratio of haemorrhagic complications changes with hyperglycaemia.

Management of feeding

Dietary regimens in the acute stroke setting should be aimed at being diabetes-friendly so as not to worsen hyperglycaemia, which is already difficult to control. As per the Joint British Diabetes Societies (JBDS, 2012) guidelines, all stroke patients with diabetes require careful monitoring of blood glucose every 4–6 hours, as they are likely to require diabetes medicine adjustment. One should aim for blood glucose levels of 6–12 mmol/L during feeding.

Problems may arise if a patient's ability to swallow has been affected by the stroke. Some

people lose the ability to swallow, either from a motor deficit in the muscles involved or a cognitive issue such as a lack of motivation or attention. When this happens, if a degree of swallowing ability is maintained, patients may require thickened fluids or puréed meals as recommended by a speech and language therapist. As this may be insufficient to meet dietary requirements, early involvement of a dietitian is key. A high-energy supplement drink, such as Fresubin Original or Fresubin 2 Kcal (Fresenius Kabi, Warrington), can be added to a feeding regimen if the individual is hypocaloric.

If swallowing is severely impaired, patients may require a temporarily placed nasogastric tube for feeding and nutrition, as well as for medicine administration. If swallowing is permanently impaired, percutaneous endoscopic gastrostomy (PEG) is another viable option. The typical feed commenced is a high-calorie feed as recommended by a nutritionist. An issue with the nasogastric tube is that not all oral diabetes medicines are compatible with it, and this may limit treatment. In such cases, suspension metformin or subcutaneous/intravenous insulin is a satisfactory substitute, as these will not be affected by impaired swallowing.

The JBDS (2012) guidelines also recommend that, if a patient was on a basal insulin regimen (glargine or detemir) before the stroke, the regimen should be continued. Should a patient require enteral feeding via nasogastric tube or PEG, first-line glycaemic management is with premixed human insulin or isophane insulin at the start or midpoint of feeding. Should hyperglycaemia remain an issue, it is advisable to start a variable-rate insulin regimen rather than administering one-off stat doses of insulin. A DSN and dietitian will best advise on diabetes regimens and nutrition, and their expertise should be sought early on.

Infection

Hyperglycaemia is known to be a risk factor for infection, as the rise in blood glucose gives a favourable environment for bacteria to proliferate in. Stroke patients are especially at risk of developing hospital-acquired or aspiration pneumonia owing to factors such as prolonged periods of immobility and impaired swallowing.

Page points

1. Hyperglycaemia can exacerbate the effects of a stroke, increase the size of the infarct and reduce the efficacy of treatments such as thrombolysis.
2. Stroke can affect a patient's ability to eat; thus, puréed food, nasogastric feeding or percutaneous endoscopic gastrostomy may be necessary to deliver nutrition, and close glycaemic monitoring is required.
3. People who are already on a basal insulin regimen should continue it in the acute stroke setting. Variable-rate insulin infusions are preferable to one-off stat doses of insulin.

Box 2. Case study of hyperglycaemia in acute stroke.

Mr S, a gentleman with type 2 diabetes, was walking back from the local grocery store when he suddenly collapsed. He was found lying on the pavement, unable to get up because his right side was feeling weak. A nearby pedestrian called for an ambulance to take him to hospital. On arrival at Accident and Emergency, Mr S was examined and found to have decreased strength in his right side, facial droop, sensory impairment on the right, slurred speech and some word-finding difficulties. His blood glucose level on admission was 20 mmol/L. Computed tomography of the head showed a left-sided parietal infarct. He was admitted to the stroke ward for rehabilitation and ongoing care, and was started on aspirin and atorvastatin for the stroke. He required frequent DSN input in the first few days because his blood glucose remained elevated despite being well controlled previously. Despite maximum oral antidiabetes therapy, he remained hyperglycaemic; therefore, he was started on a long-acting insulin. His function slowly improved throughout his stay, and he was discharged home with good functional capacity (mobility and speech). At his follow-up appointments he no longer required the long-acting insulin and was able to revert to oral therapy.

Page points

1. Hyperglycaemia can increase the risk of infection, and stroke patients have a high risk of pneumonia, pressure ulcers and urinary tract infections.
2. Acute stroke patients need close monitoring for hypoglycaemia; careful control of feeding and diabetes treatment can prevent it.
3. Outside of acute care, hypoglycaemia can often present with stroke-mimicking symptoms; resolution of hypoglycaemia can reverse these.

As the majority of people have reduced mobility secondary to stroke, they are at high risk of developing pressure ulcers as a result of being bed- or chair-bound. They may also have nutritional deficiencies that can increase the risk. These pressure sores are then also at risk of infection. Moreover, once a wound has formed, diabetic vasculopathy impairs healing via decreased blood flow and decreased granulation tissue formation. The connective tissue cells have compromised migration and proliferation capabilities, which delays their ability to travel to the wound site to repair it. Finally, if stroke leads to incontinence, either through a direct impact on the sensation or muscles involved or indirectly through a decreased level of consciousness, this increases the risk of developing a urinary tract infection. Therefore, encouragement of mobilisation, chest physiotherapy, assessment by the speech and language team, use of pressure-relieving equipment, regular turning of immobile patients and good hygiene are of paramount importance in this group of patients.

In summary, hyperglycaemia plays a crucial role in the acute stroke setting. Not only does a high glucose level impede potential treatment for ischaemic stroke but it also increases the risk of haemorrhagic events. Additionally, poorly controlled blood glucose in the acute phase expedites evolution of the infarct by damaging the surrounding penumbra. However, optimal diabetes control has not been linked to any improvement

in morbidity or mortality, but rather increases the risk of hypoglycaemia. The case study in *Box 2* illustrates the importance of optimising diabetes management following a stroke.

Hypoglycaemia

Hypoglycaemia is defined as a blood glucose level of less than 4 mmol/L (JBDS, 2012). In people who have not had a stroke, it typically presents with sweating, shakiness, anxiety, confusion, irritability, lightheadedness, tachycardia, nausea and even stroke-mimicking symptoms. However, in someone who has already had a stroke and may be neurologically impaired, these symptoms may be difficult to recognise.

Hypoglycaemia can occur for a variety of reasons, including insufficient dietary intake, alterations in type or timing of food, pauses of feeding (for physiotherapy or medications), vomiting, overdose of diabetes medications, administration of diabetes medications at a suboptimal time with regard to feeding and increased physical output (JBDS, 2012). The majority of the above causes are avoidable and can be prevented through regular monitoring and adjustment of the dietary and diabetes regimens. However, should hypoglycaemia occur, it can easily be managed through administration of sugar-rich substances such as Glucogel, Lucozade, Fortijuice or intravenous dextrose; alternatively, one can give glucagon intramuscularly (JBDS, 2012). In any case, blood glucose levels need to be monitored every 4–6 hours to prevent further such episodes and ensure that appropriate treatment is being given.

Outside the hospital setting, hypoglycaemia may often produce symptoms that mimic those of a stroke. It can cause hemiplegia, aphasia, cortical blindness, headache and sensory disturbances, as well as confusion. In the worst-case scenario, it can cause permanent brain damage, resulting in coma (Mandava et al, 2015). The pathogenesis of focal symptomatology is unclear, and the imaging abnormalities found in hypoglycaemia are very variable and weakly associated with the functional deficits. About one fifth of these episodes will mimic an acute stroke on imaging (Yong et al, 2012). That is why it is crucial to test blood glucose levels in all patients with acute neurological

impairment, as hypoglycaemia is easily reversible (Foundation for Education and Research in Neurological Emergencies, 2010). *Box 3* describes a case of suspected stroke that was revealed to be an episode of hypoglycaemia.

Summary

In summary, stroke is a commonly encountered problem amongst people with diabetes. In those who survive, it can be a life-changing event with a debilitating future. It is of great importance to optimise modifiable risk factors in view of prevention as well as during active treatment of the disease. Hypertension and diabetes are both factors which play an important role in disease likelihood and progression. Currently, studies have not proven that optimal diabetes control aids the prevention of stroke or is prognostically beneficial in acute stroke. However, as diabetes is a known risk factor for stroke, it may be beneficial to investigate this further. ■

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Box 3. Case study of hypoglycaemia mimicking stroke.

Mrs B, an elderly lady with insulin-dependent type 2 diabetes, had been fasting for Ramadan. She normally took 18 units of insulin aspart (Novomix) in the morning with breakfast. She inadvertently gave herself her usual amount of insulin without having any breakfast, and soon afterwards she became unwell. She became confused, developed right-sided weakness and her speech was impaired. Her elderly husband, who had never seen her like this before, was worried she may have had a stroke. He called for an ambulance and she was brought to Accident and Emergency. On initial assessment, she had normal observations and a blood glucose level of 2.9 mmol/L. Hypoglycaemic treatment with dextroglucagon and intravenous dextrose (10%) was immediately administered. Upon reassessment by a doctor, her symptoms had resolved and she felt much better. Clinical examination confirmed no residual weakness and normalisation of her speech.

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