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Influence of Diabetes Mellitus on Stroke

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Authors' contributions

This work was carried out in collaboration between both authors. Author HAZ wrote the first draft of the manuscript. Author PSM managed the literature searches and wrote the subsequent drafts. Both authors read and approved the final manuscript.

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ABSTRACT

Diabetes is known to be an independent risk factor for the development of stroke. Stroke accounts for 20% of deaths among patients with diabetes, and is seen more commonly in younger age group than in non-diabetics. This reflects the adverse impact on economy and constitutes a major burden on the families of these patients and the country as well. This review highlights the influence of diabetes on stroke in many aspects, aiming to share a positive input on this major health problem.

Keywords: Diabetes mellitus; stroke; hyperglycemia; prediabetes.

1. INTRODUCTION

Diabetes mellitus is considered to be a major health problem which is rising progressively due to increased rate of aging population and the sedentary lifestyle seen globally. It is a rapidly evolving global pandemic, affecting more than 300 million patients world-wide. The world health organization (WHO) estimates the prevalence of diabetes globally to be around 2.8% and the number of diabetics is anticipated to reach 366 million in 2030.

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Stroke is the second major cause of death in the world. Diabetics are at about 1.5 to 3 times the risk of stroke compared to the non-diabetics. Abnormal glycemic levels can be encountered in many clinical settings, including diabetes, impaired glucose tolerance (IGT), and stress hyperglycemia. Diabetes may be undiagnosed in a large proportion of asymptomatic people, but remains an important risk factor for stroke. Individuals with IGT remain at high risk of developing stroke and other cardiovascular insults.

Diabetes is known to be an independent risk factor for the development of stroke. Stroke accounts for 20% of deaths among patients with diabetes, and is seen more commonly in younger age group than in non-diabetics. This reflects the adverse impact on economy and constitutes a major burden on the families of these patients and the country as well. This review highlights the influence of diabetes on stroke in many aspects, aiming to share a positive input on this major health problem. Diabetes mellitus is considered to be an important cause of stroke. Patients with diabetes have double the risk of stroke than the non-diabetic group [1]. The relationship between transient ischemic attack and diabetes is less pronounced than that for completed stroke. Diabetics with peripheral vascular disease have significant risks for stroke. The duration of diabetes plays an important role in increasing the risk of stroke. It has been estimated that the risk of stroke increases by 3% per year of diabetes duration. The size of ischemic stroke increases by the state of hyperglycemia with a negative impact on the outcome post stroke. Bell has reported that the majority of ischemic strokes in diabetic patients are caused by the occlusion of small penetrating arteries, thus leading to small infarcts within the white matter [2].

2. DIABETIC AUTONOMIC NEUROPATHY

Diabetic autonomic neuropathy is another contributory factor in the development of stroke in patients with diabetes. Silent cerebral infarctions are now seen more commonly among diabetics, especially the aging population, due to the advent of CT and MRI imaging. Thus, the prevalence of stroke among diabetics is much higher now than what was believed in the past. Based on the National Hospital Discharge Survey, in the U.S. during 1989-91 there was an annual average of 327.746 hospitalizations that listed diabetes and stroke as a discharge diagnosis, representing 11.2% of all hospital discharges in which diabetes was listed. The Multiple Risk Factor Intervention Trial (MRFIT) had reported a 2.8 fold increase in the risk of mortality from stroke among patients with diabetes [3]. In a study on people of Rancho Bernardo, CA, 3778 patients were evaluated during 12 years for fatal and nonfatal stroke. The risk of stroke was significantly higher among diabetic patients than non-diabetics [4].

3. HYPERGLYCEMIA

There are many shared factors in the management of diabetes and stroke as both affect the vascular system. Diabetes as well is strongly associated with dyslipidemia and hypertension. The United Kingdom Prospective Diabetes Study (UKPDS) reported an important relation between the development of the first stroke among diabetics and the presence of other risk factors, like advanced age, systolic hypertension, smoking and atrial fibrillation. The estimated prevalence of diabetes among patients with stroke is around 10-25% and stress hyperglycemia is seen in about 60% of patients with acute stroke. UKPDS study group had developed risk engine model forecasting the absolute risk for a first stroke in patients with type 2 diabetes, using variables, like duration of diabetes, age, sex, smoking, systolic blood pressure, total cholesterol to HDL ratio and presence of AF [5]. McCall reported that hyperglycemia at admission confers a poorer prognosis after stroke in all patients in terms of morbidity and mortality [6]. Framingham follow-up study concluded that hyperglycemia is an independent risk factor for stroke [7].

Among patients who were admitted to hospital with stroke, 22.4% men and 24.7% women reported history of diabetes mellitus, as evidenced by the Minnesota Heart Survey. Barzilay et al studied 5712 patients; they screened them for diabetes and cerebrovascular accident (CVA). In those with diabetes, 12.6% of males had CVA and 12.7% of females had CVA [8]. Folsom et al. [9] had performed a study on 12000 adults, aged 45-64 years who had no cardiovascular disease at baseline, followed for 6-8 years. They reported a 3.7 times relative risk of ischemic stroke for diabetes, 1.74 for a 0.11 increment of waist to hip ratio and 1.19 for a 50 picomole per liter (pmol/l) increment of fasting insulin among non-diabetic subjects. They concluded that diabetes is a strong risk factor for ischemic stroke, as well as high waist to hip ratio and insulin resistance [9].

Pathologically, many factors have been attributed to the adverse effects of hyperglycemia on the nervous system, including small dense low density lipoprotein (LDL), low high density lipoprotein (HDL) and high triglyceride levels. Endothelial dysfunction was found to induce vasoconstriction, proinflammatory and prothrombotic mechanisms that can ultimately lead to plaque formation and rupture [10]. Large and small blood vessels are affected in diabetic patients with stroke.

Daiva R et al. conducted a prospective study with a follow-up of 17.5 years on 2295 men, aiming at identifying the risk factors for death from stroke in middle-aged Lithuanian men. They came up with diabetes; hypertension and smoking as the major risk factors for death from stroke [11]. Woo and colleagues reported that patients with acute ischemic stroke had same outcomes when they had similar blood glucose levels whether diabetics or otherwise [12]. Capes and colleagues concluded that acute hyperglycemia was a strong predictor of high mortality in patients admitted with acute ischemic stroke [13].

Jennifer E et al. studied 27269 female patients; data were pooled from 9 prospective studies in the U.S, 8.5% were diabetics, 2.9% with prior M.I and 2.3% with prior stroke. Follow-up was for 8.3 years, looking at diabetes as a cardiovascular disease risk equivalent. Conclusion was diabetic patients without cardiovascular disease have a fatal stroke risk similar to that of non- diabetics [14]. Kissela BM, et al. [15] showed that diabetes is one of the most important factors for ischemic stroke, especially in patients less than 65 years, 37-42% of all ischemic strokes in both African Americans and whites are attributed to the effects of diabetes alone or in combination with hypertension. The Copenhagen stroke study demonstrated that diabetic stroke patients were 3.2 years younger than the non-diabetic stroke patient ($p < .001$) and had hypertension more frequently (48% vs. 30%, $p < . 0001$), diabetes independently increased the relative death risk by 1.8. Conclusion was diabetes influences stroke in several aspects: in speed of recovery, age, subtype and in mortality [16].

4. A1C

In 2012, Hu et al studied 1277 patients with acute stroke, guided by A1C, they concluded that there was a strong relationship between the blood glucose level on admission and the mortality rate in those without history of diabetes. Mortality was higher in those with A1C > 7% than those with A1C < 7% [17]. Clara et al. [18] performed a study aiming to study the impact of the prestroke glycemic control on the survival of 799 patients admitted from February 15, 2005 through May 31, 2009. The survival was recorded at 30 days and one year. The relationship between A1C on admission and stroke severity was assessed utilizing a logistic regression model and survival was investigated utilizing the Cox proportional hazard regression. The mortality rate at 30 days was 7.8%, A1C was found to be a strong predictor of mortality ($p= 0.011$). They concluded that uncontrolled prestroke glycaemia is an independent factor for the adverse outcome of stroke [18].

5. GLYCEMIC CONTROL

Janusz K, et al. [19] have shown that a significant severity of changes in the carotid arteries was found in diabetic patients with stroke. Patients with diabetes and stroke require longer hospitalization and have a more severe disability at discharge. Data from the Atherosclerosis Risk in Communities (ARIC) study has confirmed the relationship between the increased levels of HbA1C and the increased relative risk of stroke in diabetic and non-diabetic patients [20]. Adequate glycemic control has a positive impact on reducing the microvascular complications but failed to show any benefit regarding stroke prevention. Intensive glycemic control during the onset of acute stroke was assessed by the Glucose Insulin in Stroke Trial (GIST), which recruited 933 patients, randomized to insulin infusion containing glucose and potassium. The trial failed to show any beneficial effects regarding morbidity and mortality [21]. Lack of benefit was attributed to hypoglycemic episodes especially with tight glycemic control seen post stroke. Hypoglycemia can lead to cognitive dysfunction through direct brain damage [22,23]. The relationship between tight glycemic control and stroke was evaluated by UKPDS, patients with type 2 diabetes in the intensive arm had no significant reduction in stroke incidence as compared to those on conventional therapy ($p=0.52$). Adequate glycemic control was associated with 4.6 times reduction in mortality [24]. Diabetes increases the risk of stroke recurrence up to 5.6 times that of non-diabetics [25]. Based on the above data, it seems that patients with diabetes have an increased risk of stroke irrespective of their glycemic control [26].

6. HYPERTENSION

Control of hypertension is associated with a significant reduction of stroke incidence among patients with diabetes mellitus. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated a 33% stroke risk reduction in 3577 diabetics with previous history of cardiovascular (CV) insults, randomized to Ramipril or placebo [27]. The perindopril protection against recurrent stroke (PROGRESS) trial showed a significant reduction of stroke in patients with diabetes when put on perindopril therapy [28]. Now, the accepted blood pressure target for diabetics is less than 140/90 [29]. The recommended agents are ACE-Is or angiotensin-receptor blockers (ARBs).

7. DYSLIPIDEMIA

Stroke prevention can be achieved through the use of anti-lipids and this association has been verified by the Heart Protection Study, using 40 mg simvastatin versus placebo. The study had been performed among high risk group [30]. The SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) confirmed the role of lowering LDL in the prevention of recurrent stroke. 4731 patients with previous stroke were enrolled and randomized to atorvastatin 80 mg daily or placebo. The intervention group showed a 16% risk reduction for stroke and a 23% reduction in transient ischemic attacks [31].

8. PARASYMPATHETIC NERVOUS SYSTEM

Patients with diabetes have decreased endothelial-dependent vasodilation, due either to decreased nitric oxide synthesis or impaired metabolism. Physiologically, nitric oxide confers a protective role against platelet aggregation and ischemia. It has been shown that parasympathetic neurons which secrete nitric oxide degenerate and die in the presence of defective insulin actions [32].

9. PLATELETS

Diabetes is regarded as a hypercoagulable state [33], due to the high levels of plasminogen activator inhibitot-1, antithrombin 111 and tissue plasminogen activator antigen, which lead to inhibition of fibrinolysis. Some studies demonstrated an up-regulation of coagulation factors VII, VIII and von Willebrand in patients with diabetes, leading to increased thrombosis and stroke incidence. The explanation of the above changes is believed to be due to the chronic inflammation induced by diabetes. The enhanced thrombosis is due to the platelet hyper-reactivity, mediated by the exaggerated response to adenosine phosphate (ADP), seen in diabetic patients [33]. Insulin inhibits platelet aggregation in response to ADP [34]; this action is defective in diabetes, resulting in higher incidence of thrombosis and stroke. Thromboxane A2 levels are higher in diabetic patients, leading to enhanced thrombotic state [34].

Carotid intima-media thickness (CIMT) was found to be increased in patients with diabetes. The Insulin Resistance Atherosclerosis Study (IRAS) has confirmed this finding; the impact of this is increased incidence of stroke. Diabetic patients with stroke have higher CIMT than those without stroke and non- diabetic patients [35]. Impact of diabetes on stroke survival was shown by some studies, demonstrating worsening functional outcome and neurological recovery in patients with diabetes [36]. Acceleration of Infarct size and progression has been seen more among diabetic patients than non- diabetics [37].

Platelets play a crucial role in atherogenesis among patients with diabetes via many factors, including; high blood glucose, hypercholesterolemia, oxidative stress, inflammatory processes, high incidence of insulin resistance and endothelial dysfunction [38]. The increased glycation of platelets leads to failure of acetylation by aspirin and these results in aspirin resistance [39]. The use of anti-platelets is essential in secondary prevention of stroke in diabetic patients, but the evidence is lacking regarding their use in primary prevention. The risk of bleeding restricts their use in primary prevention of stroke [40].

The use of aspirin and clopidogrel combination did not show any benefit in stroke prevention over aspirin alone, in fact, there was increased incidence of bleeding (the Molecular Analysis for Therapy Choice Program - MATCH trial) [41]. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study did not prove any benefit of aspirin and clopidogrel combination over aspirin alone in secondary prevention of stroke in high risk group, but did not demonstrate higher incidence of bleeding as shown by the MATCH trial [42].

Carotid endarterectomy is needed for diabetics with significant stenosis (>70%) especially in symptomatic patients, being a major stroke risk factor.

Smoking plays an important role in predisposition to stroke, so counseling is recommended in order to minimize the risk of stroke especially among diabetic patients.

The use of anti-coagulant therapy is advised in patients with chronic atrial fibrillation in order to prevent the occurrence of stroke. Warfarin is the commonly used agent but anti-thrombin medications are now emerging as alternatives [43].

10. SUSTAINED HYPERGLYCEMIA

Ntaios G et al. conducted a study aiming at testing the hypothesis that admission blood glucose in the range of 3.7- 7.3 mmol/l after ischemic stroke is associated with a favorable outcome, whereas, persistent higher blood glucose above that range at 24-48 hours following stroke has a negative impact on the outcome. The investigators reviewed all stroke cases on admission with blood glucose above 7.3 mmol/l. They divided the patients into 2 groups (those with glucose >7.3 mmol/l and < 7.3 mmol/l. Modified Rankin Score < 2 at 3 months was regarded as a favorable functional outcome. 1,984 patients with stroke were admitted between January 1, 2003 and October 20, 2009. The favorable outcome was not significantly different between the two groups (59.2% versus 48.7%). They concluded that sustained hyperglycemia above 7.3 mmol/l at 24-48 h following stroke was not shown to affect the functional outcome adversely at 3 months irrespective of diabetes status [44].

The impact of admission hyperglycemia on stroke outcome following thrombolysis in relation to reperfusion timing was studied by Alvarez-Sabin and colleagues. They reviewed 138 stroke patients with middle cerebral artery occlusion, receiving tissue plasminogen activator (IV tPA) less than 3 hours from the onset of stroke. At baseline and 24 hours, the National Institutes of Health Stroke Scale (NIHSS) scores were calculated. 37.3% of patients were hyperglycemic at baseline while 62.7% were normoglycemic. In 23% of cases reperfusion was performed in less than 3 hours of the onset of stroke, 36% of patients achieved perfusion between 3 to 6 hours, between 6-12 hours in 12% of cases. 23% of patients remained with middle cerebral artery occlusion at 12 hours. The worse outcome in relation to hyperglycemia was reported in patients with recanalization occurring <3 hours than those between 3 and 6 hours and 6-12 hours. They concluded that the adverse effect of acute hyperglycemia is more evident after early than delayed canalization [45].

11. MORTALITY

Qian Jia et al. conducted a study looking at the relationship between diabetes and mortality, recurrence and functional status following ischemic stroke. Data was retrieved from a nationwide, prospective registry, the China National Stroke Registry. The prevalence of diabetes in China is around 9.7%. The acute stroke in the registry included intracerebral bleeding, subarachnoid hemorrhage and acute ischemic stroke. The diagnosis of acute ischemic stroke was made based on the WHO criteria and confirmed by CT or MRI findings. Both type 1 and 2 diabetics were enrolled. Baseline characteristics were reviewed. The severity of stroke was assessed by the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale at the first 24 hours after admission and upon discharge. Outcomes were reassessed at 3 and 6 months following the onset of stroke. 22216 in-patients were studied, recruited from 132 hospitals. Out of 14526 patients with acute ischemic stroke, 3483 patients were diabetics (27%). The investigators showed that the majority of diabetic patients had history of stroke, unlike other studies. Urinary tract infection was seen more among diabetics in this study unlike other studies [46].

Death rate and dependency were observed more in the diabetic population than others after 6 and 12 months after stroke. This had been attributed to the presence of multiple comorbidities in patients with diabetes. The study did not consider the presence of sustained hyperglycemia during the first few days following stroke that might contribute to adverse outcomes as shown in some studies [47].

Gentile NT et al. performed a study examining the impact of glycemic control on mortality following acute stroke. They reviewed retrospectively patients discharged with the diagnosis of ischemic stroke within 40 months from a U.S. health system. Blood glucose levels and glycemic control were compared within 48 hours of hospital admission. Total number of

patients was 960 having ischemic stroke, 38.9% of them were hyperglycemic on presentation. High blood glucose level on admission was associated with increased mortality rate than normoglycemia (OR 6.54; 95% CI= 1.45 to 6.85; p= 0.004). Persistent hyperglycemia within the first 48 hours post stroke was associated with higher mortality rate (OR = 6.54; 95% CI = 2.41 to 17.87; p< 0.001). Normoglycemia conferred a 4.6-fold decrease in mortality rate compared with hyperglycemia. The authors concluded that hyperglycemia on presentation was associated with a gloomy outcome post stroke and adequate glycemic control was beneficial in terms of better survival and favorable outcome [48].

12. THROMBOLYSIS

Fuentes B and colleagues conducted an observational study analyzing the relation between acute ischemic stroke outcome and the use of intravenous thrombolysis among patients with diabetes mellitus. They reviewed 1139 in-patients with ischemic stroke; 24.8% were diabetics, 23.2% of them were treated with intravenous thrombolysis and 21.9% were non-diabetics. It has been shown that those with diabetes were older and with multiple comorbidities. Hyperglycemia was more pronounced in the diabetic group. No major differences were observed regarding intracerebral bleeding, stroke severity and mortality either acute or at 3 months. Stroke severity was linked to poor outcome in those who did not receive thrombolysis. The authors concluded that thrombolytic therapy in acute ischemic stroke was associated with better outcome among diabetics and recommended no exclusion of diabetic patients from receiving thrombolysis in case of acute ischemic stroke [49].

13. ACUTE ISCHEMIC STROKE AND HYPERGLYCEMIA

Stead LG et al studied the differences in outcome between diabetics and non- diabetic subjects visiting the emergency room with acute ischemic stroke and high blood glucose. They reviewed 447 patients reported to emergency room with acute ischemic stroke and blood glucose had been checked on the arrival. The outcomes of the study involve infarct size, severity, functional impairment and mortality at 90 days. Hyperglycemia was defined as blood glucose > 7.3 mmol/l. The investigators reported more stroke severity in those with hyperglycemia (p= 0.002) and higher functional impairment among the hyperglycemic group than those with normal blood glucose (p= 0.004), mortality at 90 days was seen to be 2.3 times more among the hyperglycemic group compared to the normoglycemic patients (p<0.001). Stroke severity and functional impairment were more pronounced in those with hyperglycemia and no past history of diabetes. They concluded that hyperglycemia at the onset of acute ischemic stroke is linked to poorer outcome in those without history of diabetes than those with diabetes [50].

Kuwashiro and colleagues conducted a study looking at the predisposing factors for the outcome 1 year post stroke among patients with diabetes. They had enrolled 452 diabetic patients and their characteristics and outcome 1 year post stroke were reviewed prospectively. Modified Rankin Scale score> 2 represents the poor outcome 1year post stroke. 286 patients were with good outcome, 166 patients with poor outcome. Increasing age per 1-year increase, NIHSS score on presentation per 1- point increase, diabetic nephropathy and A1C, per 1% increase were regarded as independent factors for poor outcome after 1 year post stroke in diabetic population [51].

14. HYPERGLYCEMIA ON ADMISSION

Stead LG et al performed a study with a view to examine the relationship between hyperglycemia on admission and early mortality and adverse outcome following intracerebral hemorrhage. It was a cohort study involving 237 patients reported to emergency department (ED) with intracerebral hemorrhage, their blood glucose was checked. Outcome comprised of size of hematoma, stroke severity, intraventricular extension of the hematoma (IVE), functional capacity at discharge and date of death. 47 patients were diabetic and showed higher blood glucose levels than the non-diabetics (median 202 mg/dl for diabetics vs 132.5 mg/dl for non-diabetics<0.0001). High blood glucose was associated with early mortality in both groups, poor functional outcome in non-diabetics. Hematoma volume, intraventricular extension of bleeding, high blood glucose on presentation were important predictors of death (p= 0.0031). They concluded that hyperglycemia on arrival was an independent predictor of early death and adverse functional outcome among non-diabetics with intracerebral bleeding [52].

15. PREDIABETES

Tanaka R, et al. [53] studied the relationship between diabetes and prediabetes and short-term outcome in patients with acute ischemic stroke. They enrolled 242 patients with ischemic stroke. GTT with 75-g was provided to 116 patients who were not known diabetics before. 140 patients were diabetics, 52 patients were pre-diabetics and 50 patients were normoglycemics. NIHSS S and modified Rankin Scale score were used to evaluate the early neurological deterioration in the first 2 weeks and the poor short-term outcome respectively. The early neurological deterioration was higher in patients with diabetes compared to normoglycemic patients (ORs= 11.354; 95%CI, 1.492-86.415; P=0.026). Regarding the pre-diabetic group, the association was found insignificant; p=0.093. Patients with diabetes showed poorer outcome compared with the normoglycemic group (ORs 3.667; 95% CI, 1.834- 7.334; P < 0.001). Likewise, the association between prediabetics and normoglycemics was insignificant regarding the poor outcome (ORs 2.058; 95% CI, 0.916- 4.623; P=0.08). The authors concluded that both diabetes and pre-diabetes were linked to poor early outcome post-acute ischemic stroke [53].

16. CONCLUSION

Based on the above and evidenced by studies, diabetes is significantly influencing all aspects of stroke, from etiology to mortality.

Much effort has to be exerted in diabetes prevention, aiming at reducing the incidence, devastating effects and economic burden of stroke.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Banerjee C, Moon YP, Paik MC. Duration of diabetes and risk of ischemic stroke. The Northern Manhattan Study. Stroke. 2012;43:1212-1217.
2. Bell DSH. Stroke in the diabetic patient. Diabetes Care. 1994;17:213-19.
3. Stamler J, Vaccaro O, Neaton JD. Wentworth D, for the MRFIT research group: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care. 1993;16: 434-44.
4. Barren- Conner E, Khaw K-T. Diabetes mellitus: An independent risk factor for stroke? Am J Epidemiol. 1988;128:116-23.
5. Kothari V, Steven RJ, Adler AL, Stratton IM, Manley SE, Neil HA, Holman RR. UKPDS 60: Risk of stroke in type 2 diabetes estimated by the UKPDS risk engine. Stroke. 2002;33:1776-1781.
6. McCall AL. The impact of diabetes on the CNS. Diabetes. 1992;41:557-70.
7. Kennel WB, Wolf PA, Garrison RJ (Eds). The Framingham study. An epidemiological investigation of cardiovascular disease. U.S. Department of Health and Human Services. National Heart, Lung and Blood Institute. NIH publ. no. 1987;87:2703.
8. Barzilay JI, Spiekerman CF, Kuller LH, et al. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: The cardiovascular health study. Diabetes Care. 2001;24(7):1233-1239.
9. Folsom AR, Rasmussen ML, Chambless LE, Cooper LS, Schmidt MI, Heiss G. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke: The Atherosclerosis Risk in Communities (ARIC) study investigators. Diabetes Care. 1999;1077-1083.
10. Castilla-Guerra L, Del Carmen Fernandez-Moreno M. Stroke in diabetic patients: Is it really a macrovascular complication? Stroke. 2007;38(10):106.
11. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartianen E. Diabetes mellitus as a risk factor for death from stroke: Prospective study of the middle- aged finnish population. Stroke. 1996;27:210-215.
12. Woo J, Lam CWK, Kay R, Wong AHY, Teoh R, Nicholls MG. The influence of

hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. Archives of Neurology. 1990;47(11):1174-1177.

13. Capes SF, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in non-diabetic and diabetic patients: A systematic overview. Stroke. 2011;32(10)2426-2432.
14. Ho JE, Paultre F, Mosca L. Is diabetes mellitus a cardiovascular disease risk equivalent for fatal stroke in women? Data from the Women's Pooling Project. Stroke. 2003;34:2812-2816.
15. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schnider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, Gebel J, Shukla R, Broderick JP. Epidemiology of ischemic stroke in patients with diabetes: The greater Cincinnati/ Northern kentucky stroke study. Diabetes Care. 2005;28:355-359.
16. Jorgensen H, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes: The copenhagen stroke study. Stroke. 1994;25:1977-1984.
17. Kamouchi M, Matsuki T, Hata J, et al. Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: The fukuoka stroke registry. Stroke. 2011;42(10):2788-2794.
18. Clara Hjamarsson, Karin Manhem, Lena Bokemark, Bjorn Andersson. The role of prestroke glycemic control on severity and outcome of acute ischemic stroke. Stroke Research and Treatment; 2014, Article ID 694569.
19. Karapanayiotides T, Piechowski- Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. Neurology. 2004;62:1558-1562.
20. Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR. Glycaemia (hemoglobin A1C) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Lancet Neurol. 2005;4:821-826.
21. Gray CS, Hildreth AJ, Sandercock PA, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycemia: The UK glucose insulin in stroke trial (GIST-UK). Lancet Neurology. 2007;6(5):397-406.
22. Johnston KC, Hall CE, Kissela BM, Bleck TP, Conaway MR. Glucose regulation in acute stroke patients (grasp) trial: A randomized pilot trial. Stroke. 2009;40(12): 3804-3809.
23. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby V. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. Journal of the American Medical Association. 2009;301(15):1565-1572.
24. Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J. Decreased mortality by normalizing blood glucose after acute ischemic stroke. Acad Emerg Med. 2005; 13:174-180.
25. Haney GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, Stewart-Wynne EG. Long-term risk of first recurrent stroke in the Perth community stroke study. Stroke. 1998;29:2491-2500.
26. Effect of intensive blood – glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34): UKPDS Group. Lancet. 1998;352:854-865.
27. Heart Outcomes Prevention Evaluation Study Investigators. Effects of Ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. The Lancet. 2000;355(9200):253-259.
28. Berthet K, Neal BC, Chalmers JP, et al. Reductions in the risk of recurrent stroke in patients with and without diabetes: The PROGRESS trial. Blood Pressure. 2004;13(1):7-13.
29. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. New England Journal of Medicine. 2010;362:1575-1585.
30. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. The Lancet. 2004;363(9411): 757-767.
31. Amarenco P, Benavente O, Goldstein LB, et al. Results of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405-1409.

32. Maejima K, Nakano S, Himeno M, Tsuda S, Makiishi H, Ito T, Nakagawa A, Kigoshi T, Nishio M, Uchida K. Increased basal levels of plasma nitric oxide in type 2 diabetic subjects: Relationship to microvascular complications. J Diabetes Complications. 2001;15:135-143.
33. Meigs JB, Mittleman MA, Nathan DM, Toffler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PW. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: The Framingham Offspring study. JAMA. 2000;283:221-228.
34. Halushka PV, Rogers RC, Loadholt CB, Colwell JA. Increased platelet thromboxane synthesis in diabetes mellitus. J Lab Clin Med. 1981;97:87-96.
35. Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S. Correlation between common carotid arterial wall thickness and ischemic stroke in patients with type 2 diabetes mellitus. Metabolism. 2002;51:244-247.
36. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE. Admission glucose level and clinical outcomes in the NINDS rt- PA stroke trial. Neurology. 2002;59:669-674.
37. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davies SM. Persistent post- stroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208-2214.
38. Ferroni P, Bassili S, Falco A, Davi G. Platelet activation in type 2 diabetes mellitus. Journal of Thrombosis and Haemostasis. 2004;2(8):1282-1291.
39. Gasparyan AY, Watson T, Lip GYH. The role of Aspirin in cardiovascular prevention: Implications of Aspirin resistance. Journal of American College of Cardiology. 2008; 51(19):1929-1843.
40. Zhang C, Sun A, Zhang P. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Research and Clinical Practice. 2010;87(2):211-218.
41. Diener PHC, Bogousslavsky PJ, Brass PIM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): Randomized, double- blind, placebo- controlled trial. The Lancet. 2004;364(9431):331-337.
42. Bhatt DI, Fox KAA, Hacker W, et al. Clopidogrel and Aspirin versus aspirin alone for the prevention of atherothrombotic events. New England Journal of Medicine. 2006;354(16):1706-1717.
43. Connolly SJ, Ezekowitz MD, Yusuf S. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009;361:1139-1151.
44. Ntaios G, Abatzi C, Alexandrou M, Lambrou D, Chatzopoulos S, Egli M, Ruiz J, Bomstein N, Michel P. Persistent hyperglycemia at 24-48 h in acute hyperglycemic stroke patients is not associated with a worse functional outcome. Cerebrovascular Diseases. 2011;32(6):561-566.
45. Alvarez-Sabin J, et al. Impact of admission hyperglycemia on stroke outcome after thrombolysis: Risk stratification in relation to time to reperfusion. Stroke. 2004; 35(11):2493-8.
46. Chen SL, Jackson SL, Boyko EJ. Diabetes mellitus and urinary tract infection: Epidemiology, pathogenesis and proposed studies in animal models. J Urol. 2009;19: 123-129.
47. Fuentes B, Ortega- Casarrubios M, San Jose B, Castillo J, Leira R, Serena J, et al. Persistent hyperglycemia> 155 mg/dl in acute ischemic stroke patients: How well are we correcting it? Stroke. 2010;41: 2362-2365.
48. Gentile NT, Seftchick MW, Huynh T, Kruus IK, Gaughan J. Decreased mortality by normalizing blood glucose after acute ischemic stroke. 2006;13(2):174-180.
49. Fuentes B, et al. Acute ischemic stroke patients with diabetes should not be excluded from intravenous thrombolysis. J Thromb Thrombolysis. 2014;38(4):522-7.
50. Stead LG, Gilmore RM, Belloio MF, Mishra S, Bhagra A, Vaidyanathan L, Decker WW, Brown RD Jr. Hyperglycemia as an independent predictor of worse outcome in non-diabetic patients presenting with acute ischemic stroke. Neurocrit Care. 2009; 10(2):181-6.
51. Kuwashiro T, et al. The impact of predisposing factors on long-term outcome after stroke in diabetic patients: The fukuoka stroke registry. Eur J Neurol. 2013;20(6):921-7.

52. Stead LG, et al. Emergency Department hyperglycemia as a predictor of early mortality and worse functional outcome after intracerebral hemorrhage. Neurocrit Care. 2010;13(1):67-74.

53. Tanaka R, et al. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. Journal of the Neurological Sciences. 2013; 32(1):45-50.

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