Relationship between Diabetes and Ischemic Stroke: Analysis of Diabetes-Related Risk Factors for Stroke and of Specific Patterns of Stroke Associated with Diabetes Mellitus

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Abstract

Diabetes and ischemic stroke are common diseases that frequently occurring together. Among patients with diabetes mellitus several factors contribute in varying degrees to the overall cerebrovascular risk including hyperglycemia, vascular risk factors such as hypertension and dyslipidemia and also genetic, demographic, and lifestyle factors and several studies have shown that people with diabetes have approximately twice the risk of ischemic stroke compared with those without diabetes. The association between ischemic stroke and diabetes is bidirectional and it is not limited to acute ischemic stroke since diabetes may contribute to a more insidious brain damage represented by lacunar infarcts increasing the risk of dementia and leading to a steeper decline in cognitive function. The higher cerebrovascular risk profile of subjects with diabetes mellitus emphasizes the importance of secondary prevention strategies with the aim to prevent a substantial number of these disabling strokes among patients with diabetes. In this review, we describe the relationship between glucose metabolism and acute ischemic stroke and focus on the analysis of diabetes-related risk factor for stroke and on specific patterns of stroke type associated with diabetes.

Keywords: Diabetes; Stroke; Cerebrovascular diseases

Introduction

Stroke is defined by focal neurological signs or symptoms thought to be of vascular origin that persisted for >24 h confirmed by brain CT and/or MRI in baseline conditions and brain CT with contrast medium after 48–72 hours and worldwide, it represents the second most common cause of mortality and the third most common cause of disability in developed countries. The two broad categories of stroke are ischemic stroke due to thrombosis, embolism, or systemic hyperfusion and hemorrhagic stroke due to Intracerebral Hemorrhage (ICH) or Subarachnoid Hemorrhage (SAH). Each of these categories can be also divided into several subtypes that have different causes, clinical pictures outcomes, and treatment. The most common cause of stroke is represented by cerebral ischemia and approximately 80 percent of strokes are due to ischemic cerebral infarction and 20 percent to brain hemorrhage. According with TOAST classification is possible to distinguish various subtypes of ischemic stroke: 1) Large Artery Atherosclerosis (LAAS); 2) Cardioembolic Infarct (CEI); 3) Lacunar Infarct (LAC); 4) Stroke of other Determined Etiology (ODE); 5) Stroke of Undetermined Etiology (UDE). The great majority of ischemic strokes are due to cardioembolism and large-artery atherosclerotic disease and approximately the 25% of all ischemic strokes are lacunar type. Several risk factors contribute to the development of ischemic stroke including hypertension, smoking, dyslipidemia and last but not least diabetes mellitus. Diabetes mellitus is one of the most common endocrine disorders affecting almost 6% of the world’s population and represent one of the most important public health challenges to all nations. It can be defined as a metabolic disorder characterized by chronic hyperglycemia associated with impaired glucose, lipid and protein metabolism and it is a leading cause of renal failure, coronary heart disease, non-traumatic lower limb amputations, and visual impairment. Diabetes and ischemic stroke are common diseases that frequently occurring together. Diabetes is an important risk factor for ischemic stroke and the association between these two conditions has been analyzed by several studies. Previously the Framingham study [1] found a 2.5-fold incidence of ischemic stroke in men with diabetes mellitus and a 3.6-fold one in women with diabetes mellitus. A multicenter cohort study from Italy [2], the DIA study (including 14,432 participants) conducted with the aim to assess the prevalence and incidence of stroke and the role of other risk factors in unselected type 2 diabetes mellitus populations showed that during a 4-year follow-up, 296 incident stroke events were recorded. In persons with no history of cardiovascular disease, the age-standardized incidence of stroke (per 1000 person-years) was 5.5 (95% confidence interval, 4.2 to 6.8) in men and 6.3 (95% confidence interval, 4.5 to 8.2) in women. In persons with a history of cardiovascular disease, it was 13.7 (95% confidence interval, 7.5 to 19.8) in men and 10.8 (95% confidence interval, 7.3 to 14.4) in women. These results underline that the incidence rates of stroke that were observed in this study confirm the importance of this event in subjects with diabetes mellitus. Indeed the incidence of stroke in this cohort is 2-3 times higher than that observed in the populations without diabetes. In addition, authors have also found that the combined role of Hba1c, microvascular complications, low HDL cholesterol, and treatment with insulin plus oral agents highlights the importance of diabetes mellitus history and clinical background in the development of stroke. The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) [3], conducted with the aim to describe the epidemiology of ischemic stroke in a biracial population of patients with diabetes residents in the Greater
Cincinnati/Northern Kentucky region, which includes two southern Ohio counties and three contiguous northern Kentucky counties that border the Ohio River, showed that diabetes is clearly one of the most important risk factors for ischemic stroke, especially in those patients less than 65 years of age. Furthermore some authors [4], with the aim to quantify the associations of diabetes mellitus and fasting glucose concentration with risk of Coronary Heart Disease (CHD) and major stroke subtypes, have conducted a meta-analysis of individual records of diabetes, fasting blood glucose concentration, and other risk factors in people without initial vascular disease from 102 prospective studies (including 530083 participants). They found that diabetes confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes, independently from other conventional risk factors. In this analysis the reported hazard ratio for ischemic stroke was 2.3 (95% CI 2.0–2.7) in people with versus those without diabetes and assuming a population-wide prevalence of diabetes of around 10%, these findings indicate a diabetes-attributable risk of stroke of around 12%. The risk of stroke associated with diabetes is assessed predominantly in people with type 2 diabetes, because in the age group in which most strokes take place, type 2 diabetes is much more common than type 1 diabetes. The risk of stroke in patients with type 1 diabetes has been assessed in few epidemiological studies and usually with limited sample size, and the results have been inconsistent. Nevertheless with regard of this issue Janghorbani et al. [5] conducted a study with the aim to examine the relationship between type 1 and type 2 diabetes and risk of stroke subtypes in women. In this study authors showed that both type 1 and type 2 diabetes are associated with substantially increased total and most subtypes of stroke and also that the association between stroke and type 1 diabetes was stronger and this was probably attributable to younger age at onset, longer duration of diabetes, insulin deficiency, and development of hypertension with diabetic nephropathy, disturbances of coagulation-fibrinolytic parameters, increased platelet adhesiveness, or episodes of hypoglycemia. Therefore, the results of this study as well as others [6] that enable the direct confrontation between the two types of diabetes have shown that the relative risk of stroke in people with type 1 diabetes is at least similar or perhaps even higher in subjects with type 2 diabetes. The results of all these studies [1-4] confirm that subjects with diabetes mellitus have approximately twice the risk of ischemic stroke compared with those without diabetes and then underline that diabetes mellitus is an important risk factor for ischemic stroke. Furthermore, an important concept to emphasize is that the association between ischemic stroke and diabetes is bidirectional. Moreover, acute stroke may lead to abnormalities in glucose metabolism, which in turn could influence the outcome. In addition, in the context of cerebrovascular disease, diabetes may contribute to a more insidious brain damage represented by the diseases of Small Cerebral Vessels (SVD) such as lacunae or White Matter Hyperintensity (WMH) increasing the risk of cognitive decline and dementia [7] suggesting that the relationship between impaired glucose metabolism and cerebrovascular disease is not limited to acute ischemic stroke.

Risk Factors of Stroke Associated with Diabetes

Among patients with diabetes several risk factors play a role together to promote the development of ischemic stroke. In the analysis of these risk factors can be identified diabetes-specific factors such as hyperglycemia and vascular risk factors such as hypertension and dyslipidemia [8-10]. In addition to these also genetic, demographic, and lifestyle factors contribute in varying degrees to the overall risk of the subjects with diabetes mellitus [11-15]. However the risk of ischemic stroke in patients with diabetes is twice those without diabetes, even after adjustment for risk factors listed above (hazard ratio 2.2, 95% CI 1.9–2.6) [4].

Role of Chronic Hyperglycemia

As is well known, prolonged hyperglycemia is associated with microvascular complications, such as retinopathy, neuropathy, and nephropathy, and with macrovascular complications such as cerebrovascular and cardiovascular events and Peripheral Arterial Disease (PAD) caused by atherosclerosis [16,17]. Hyperglycemia contributes to the pathogenesis of macrovascular complications through several possible pathways including the generation of large amounts of Reactive Oxygen Species (ROS) such as superoxide anions which may lead to the endothelial dysfunction by reducing the bioavailability of endothelium-derived NO, formation of Advanced Glycosylation End Products (AGEs) that by binding to their receptors accelerates the atherosclerotic process by promoting LDL uptake and oxidation leading to foam cell formation and finally the diversion of glucose into the aldose reductase pathway and the activation of one or more isozymes of protein kinase C (PKC) (18-22). These changes, in their complexity, leading to the typical diabetic milieu that is characterized by a chronic state of low-grade inflammation, endothelial dysfunction, hypercoagulability, dyslipidemia and insulin resistance. However, although it is well known the harmful role of prolonged hyperglycemia in the development of micro and macrovascular complications of diabetes, until now there are no evidence to show that stroke prevention will be improved by intensive glucose-lowering treatment, in people with either type 1 or type 2 diabetes [23].

Role of Hyperglycemia in Acute Ischemic Stroke

On the other hand, deserves a separate mention, the pathogenetic and prognostic role of hyperglycemia in the acute phase of ischemic stroke. Hyperglycemia arises in 30–40% of people with acute ischemic stroke both in patients with diabetes mellitus than in patients without a previous history of diabetes and, although in some patients reflects a pre-existing and unrecognized diabetes, more often it is can be considered as a stress reaction resulting in the increased production of stress hormones such as cortisol and epinephrine following the activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system which finally results in an increased production of glucose through the gluconeogenesis, glycogenolysis, lipolysis and proteolysis. In animal models of reversible focal brain ischemia, hyperglycemia consistently increased infarct size and several mechanisms have been identified through which hyperglycemia could aggravate cerebral damage in ischemic stroke. These include the altered recanalization that has been attributed to disorders in coagulation and in fibrinolytic pathways mediated by hyperglycemia [24,25], the decreased reperfusion of the damaged brain area caused by the disturbances in metabolism of endothelium-derived nitric oxide and last but not least the increased reperfusion injury which is the result of the detrimental effects of oxidative stress and inflammation [26]. The effects of the above mentioned mechanisms alter the recovery of the ischemic penumbra that is the part of the ischemic area which may still potentially recover if proper reperfusion is restored within hours after stroke onset. On this basis, some authors [27] systematically reviewed the published literature to summarize the available evidence and to estimate the strength of the association between admission hyperglycemia and both short-term mortality and functional recovery after stroke with the aim to evaluate if stress hyperglycemia may be associated with increased mortality and poor recovery in people with diabetes and in patients without diabetes after stroke. They found that compared with patients with norm glycaemia, the unadjusted relative
risk of in-hospital or 30-day mortality after an ischemic stroke in individuals who are hyperglycemic at admission is 3-3 (95% CI 2.3–4.7) in those without known diabetes and 2.0 (0.04–90.1) in those with a known history of diabetes and concluded that acute hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke in patients without diabetes and increased risk of poor functional recovery in non-diabetic stroke survivors. Furthermore other studies [28,29] suggest that the association between hyperglycemia and poor outcome after stroke is stronger in patients with large-vessel thromboembolic stroke than in those with lacunar stroke and this is understandable considering that hyperglycemia primarily exerts its detrimental effects at the level of the ischemic penumbra which is usually not present in lacunar subtype. The detected relationship between hyperglycemia and poor outcome in patients with ischemic stroke arouses the question of whether the outcome may be improved by glucose-lowering treatment. In fact, although it is true that the concentrations of glucose can be reduced by several treatment regimens of insulin, one has to consider that in the early days after the onset of stroke the realization of normal blood glucose concentrations may be difficult probably because the intake of oral food causes fluctuations in the levels of glucose. Therefore, the achievement of stable normoglycemia in the acute phase of stroke can be difficult and the possibility of hypoglycemia remains a concern, because even with intensive monitoring, many patients may experience one or more episodes of hypoglycemia [30,31]. Findings of randomized controlled trials specifically targeting individuals with stroke have failed to show beneficial effects. In a meta-analysis of 1296 patients with acute stroke from seven trials, intensively monitored intravenous insulin treatment (aimed at maintenance of glucose concentrations between 4.0 and 7.5 mmol/L) was compared with usual care [32]. No difference was seen with respect to poor outcome (odds ratio 1.0, 95% CI 0.8–1.3), and the risk of symptomatic hypoglycemia was significantly higher in the group treated with insulin (25.9, 9.2–72.7). Therefore, there is evidence suggesting that that glucose-lowering treatment improves clinical outcome in patients with acute ischemic stroke and to date uncertainty persists about the issue of whether glucose-lowering treatment for early stroke can improve clinical outcome.

Role of Hypertension

Hypertension is defined, according to the 1993 World Health Organization criteria, like a systolic blood pressure 140 mm Hg and/or diastolic blood pressure 90 mm Hg in subjects who are not taking antihypertensive medication. Diabetes mellitus and hypertension are both common diseases and they represent two powerful independent risk factors for cardiovascular, renal and atherosclerotic disease. The pathogenesis of hypertension in diabetes type 1 and type 2 is different. Diabetic nephropathy is considered to be the main factor that contributes to the development of hypertension in patients with diabetes mellitus type 1. In the case of type 2 diabetes mellitus, hypertension is more often essential and it is part of a plurimetabolic syndrome in a context of insulin resistance. In all cases, hypertension worsens the prognosis of patients, increasing the risk of both macrovascular and microvascular complications. In patients with type 2 diabetes, lowering of blood pressure has a large effect on risk of future stroke as suggested by a recent meta-analysis [8] of 37 736 patients (13 trials) with type 2 diabetes, impaired fasting glucose or impaired glucose tolerance that assessed the effects of blood pressure control (≤ 135 mm Hg vs ≤ 140 mm Hg). Intensive blood pressure control was associated with a 10% reduction in all-cause mortality (odds ratio, 0.90; 95% confidence interval, 0.83 to 0.98), a 17% reduction in stroke, and a 20% increase in serious adverse effects, but with similar outcomes for other macrovascular and microvascular (cardiac, renal, and retinal) events compared with standard blood pressure control. In addition, a more intensive blood pressure control (≤ 130 mm Hg) was associated with a greater reduction in stroke, but did not reduce other events and also increase the risk of serious adverse events with no benefit for other outcomes. Therefore, one basis of these evidences the authors suggests that in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, a systolic BP treatment goal of 130 to 135 mm Hg is acceptable.

Role of Dyslipidemia

Dyslipidemia is one of the major risk factors for cardiovascular and cerebrovascular disease in diabetes mellitus. The defects in the synthesis and clearance of plasma lipoproteins are among the most commonly metabolically abnormal conditions that accompany diabetes. The diabetic dyslipidemia, a characteristic pattern characterized by the presence of low levels of High Density Lipoprotein (HDL) cholesterol, hypertriglyceridemia, and postprandial lipemia and which is observed more frequently in type 2 diabetes, is one of several factors that contribute to accelerating macrovascular disease in subjects with diabetes mellitus. Among the different factors involved in developing of diabetic dyslipidemia should be considered: insulin effects on liver apoipoprotein production, regulation of Lipoprotein Lipase (LpL), actions of Cholesteryl Ester Transfer Protein (CETP), and peripheral actions of insulin on adipose and muscle. The acknowledgment and treatment of dyslipidemia are therefore two important elements in the framework of a multidisciplinary approach aimed at the prevention of cerebrovascular and cardiovascular events in people with diabetes. In this regard, several studies aimed to assess the effectiveness of strategies for primary and secondary prevention of major cardiovascular events in patients with type 2 diabetes. A post hoc analysis of the Heart Protection Study [9] showed that a daily dose of 40 mg of simvastatin administered to 5963 patients with type 2 diabetes, of which about half did not have any diagnosed occlusive arterial disease at entry, was associated with a 28% (95% CI 8–44) reduction of ischemic stroke, independent of baseline lipid levels. Furthermore, in a multicentre randomised placebo-controlled trial [Collaborative Atorvastatin Diabetes Study (CARDS)] [10] authors found that daily use of 10 mg atorvastatin was associated with a 37% [17–52] reduction in cardiovascular events and with a 48% [11–69] reduction in all types of stroke.

Metabolic Syndrome and Ischemic Stroke

The term "metabolic syndrome" (MetS) define a cluster of several risk factors for cardiovascular disease including elevated blood pressure, elevated blood glucose, obesity, and dyslipidemia. There are several definitions for the MetS, The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [33] is the most widely used because of its ease of use and relation to increased risk of coronary artery disease. It is based on the presence of 3 of the following components: high fasting glucose, high blood pressure, low high-density lipoprotein cholesterol, high triglycerides, and abdominal obesity. Data from the National Health and Nutrition Examination Survey III (NHANES) [34] estimate that 47 million persons in the United States have the MetS and its prevalence is still increasing, in fact using data from the NHANES 1999 to 2002 database, 34.5 percent of participants met ATP III criteria for the metabolic syndrome compared with 22 percent in NHANES III (1988 to 1994) [35]. In addition, MetS, defined by the 2005 revised ATP III criteria, was assessed in 3323 Framingham Heart Study participants, ages 22 to 81, who did not have diabetes or Cardiovascular Disease (CVD) at a baseline examination in the early 1990s [36]. The relationship between MetS and stroke was evaluated by several studies. On this purpose, with the aim to investigate the relation...
between the MetS and risk of ischemic stroke and vascular events in the urban community–based, multiethnic, prospective cohort of the Northern Manhattan Study (NOMAS), a total of 3298 subjects were recruited and enrolled between 1993 and 2001 [37]. The authors found a significant association between the MetS and ischemic stroke risk, independent of other confounding factors including age, education, physical activity, alcohol use, and current smoking. Although the MetS is often considered a prediabetic condition and diabetes is a major risk factor for ischemic stroke, the association of the MetS without diabetes with incident ischemic cerebrovascular events has not been studied in depth, and therefore, some authors [38] conducted a study with the aim to assess the prevalence of the MetS in a large cohort of patients with atherosclerotic cardiovascular diseases and to explore the relation of MetS versus frank diabetes with first-ever ischemic stroke or Transient Ischemic Attack (TIA). The results of this study showed that, after adjusting for stroke risk factors, patients with MetS without diabetes exhibited a 1.49-fold increased odds for ischemic stroke or TIA (95% confidence interval [CI], 1.20 to 1.84), whereas those with frank diabetes had a 2.29-fold increased odds (95% CI, 1.88 to 2.78) and thus the presence of MetS even without diabetes increase in the risk of ischemic stroke or TIA and this implies that identification of the MetS in this high-risk category of patients, even before the occurrence of diabetes, could identify patients at a greater risk of ischemic cerebrovascular event. Although it is well known that MetS is associated with an increased risk of the subsequent development of cardiovascular disease or stroke, a study conducted by Hyung-Min Kwon et al. [39] showed that MetS was significantly associated with Silent Brain Infarction (SBI) independently of traditional cardiovascular risk factors suggesting that MetS has clinical utility in terms of identifying patients at increased risk of SBI and also the importance to develop strategies for controlling this syndrome and its component conditions. The MetS comprises a cluster of abnormalities that occur as a result of perturbations in multiple metabolic pathways, leading to hyperinsulinemia, insulin resistance, hyperglycemia, atherogenic dyslipidemia, and hypertension. The root causes of the syndrome appear to be multiple and include obesity (especially abdominal obesity), physical inactivity, insulin resistance, aging, and genetics. Several studies have also shown that the MetS is a proinflammatory condition associated with elevated levels of C-reactive protein (CRP), interleukin (IL)-6, and plasminogen activator inhibitor (PAI)-1 [40]. In this regard, Tuttolomondo et al. [41-46] conducted a study with the aim to evaluate the associations between arterial stiffness indexes and immune-inflammatory markers in subjects with acute ischemic stroke with and without MetS. The authors observed a higher median plasma values of immuno-inflammatory markers in subjects with acute ischemic stroke and MetS and they also found a more significant positive correlation between Pulse Wave Velocity (PWV) and immuno-inflammatory markers in acute ischemic stroke patients and MetS in relation of each TOAST subtype. On this basis authors concluded that stroke subjects with acute ischemic stroke and MetS showed a higher degree of immuno-inflammatory and arterial stiffness indexes possibly due to metabolic background of these types of patients that trigger a more intense immune-inflammatory activation irrespective of stroke subtype, whereas being related to stroke subtype in subjects without metabolic syndrome. In the context of the relationship between the MetS and stroke, an important component is represented by insulin resistance which represents the clinical expression of the inability of endogenous insulin to enhance glucose uptake and its utilization and it is the physiopathological main factor able to induce the MetS. Insulin resistance is also common among nondiabetic individuals such as elderly persons, certain ethnic groups, and persons with hypertension, obesity, physical deconditioning, and vascular disease. Insulin resistance is also associated with numerous metabolic, hematologic, and cellular events that promote atherosclerosis and coagulation. Although insulin resistance and hyperinsulinemia play a crucial role in the pathogenesis of atherosclerosis, little is known about their roles in ischemic stroke. On this basis the association between insulin resistance and risk for stroke has been examined by some authors [47] in four case-control studies and five prospective observational cohort studies. They found that six of the nine studies were methodologically sound and provide evidence that insulin resistance is associated with risk for stroke and thus concluded that insulin resistance may be considered as a prevalent risk factor for stroke. Finally, the MetS is an important risk factor for subsequent development of type 2 diabetes, cardiovascular disease and stroke and represents an increasingly common condition which therefore requires the identification and treatment of individual risk factors including an aggressive lifestyle modification focused on weight reduction and increased physical activity.

Patterns of Stroke Type Associated with Diabetes Mellitus

Diabetes and ischemic stroke are common diseases that frequently occurring together. Several studies [1-4] that have analyzed the relationship between these two disorders have shown that subjects with diabetes mellitus have approximately twice the risk of ischemic stroke compared with those without diabetes underlying that diabetes mellitus is a well-established independent risk factor for stroke and is associated with high mortality. It is well known that diabetes mellitus may contribute to systemic and intracranial atherosclerotic disease and this increased risk has been linked to the pathophysiological changes seen in the cerebral vessels of patients with diabetes [48]. With the purpose to characterize stroke patterns in stroke patients with and without diabetes mellitus Salah-Eddine Meagheri et al. [49] conducted a study in a large European sample of hospitalized stroke patients. Data from this large prospective European multicenter study showed that stroke in patients with diabetes mellitus was different from stroke in non patients from several perspectives in fact in stroke patients with diabetes mellitus, the frequency of intracerebral hemorrhage was lower, the rate of lacunes was higher, recovery of handicap by Rankin Scale score was worse, and mortality was not increased. Therefore the great contribution of this study was to demonstrate that the subtype of stroke that is mainly found among patients with diabetes is the lacunar type. These results are consistent with those of Th. Karapanayiotides et al. [50] that assessed the risk factors, etiology, lesion topography, clinical features, and outcome of all the subjects with diabetes mellitus in the Lausanne Stroke Registry (LSR). They found that diabetes mellitus was associated with lower relative prevalence of intracerebral hemorrhage (ICH; odds ratio [95% CI]: 0.63 [0.45 to 0.9]; p = 0.022), higher relative prevalence of subcortical infarction (SCI; 1.34 [1.11 to 1.62]; p = 0.009), and higher relative frequency of small-vessel (SVD; 1.78 [1.31 to 2.32]; p = 0.012) and large-artery (LAD; 2.02 [1.31 to 2.02]; p = 0.002) disease. The results of the large population studies mentioned above show that stroke patients with diabetes mellitus are associated with specific patterns of stroke type, especially with lacunar infarcts which are defined as non cortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery accounting for a quarter of all ischemic stroke. Lacunar stroke also represent the major cause of progressive motor deficits and may contribute to increase the risk of dementia and lead to a steeper decline in cognitive function constituting a significant disease, with important clinical implications. The pathogenic plausibility of the relationship between diabetes and lacunar stroke is supported by pathological and autopsy reports.
Although diabetes mellitus increases the risk of stroke, and the pathophysiological changes of diabetic cerebral vessels may differ in comparison with non-diabetic ones, the clinical and prognostic profile of stroke in people with diabetes is not yet fully understood. On this basis, Turtolomondo et al. [53-58] conducted a study to evaluate cerebrovascular risk factor prevalence in stroke patients with diabetes mellitus in comparison with subjects without diabetes with the aim to analyze whether subjects with diabetes mellitus have a different prevalence of stroke subtypes as classified by the TOAST classification, and to determine whether people with diabetes and patients without diabetes have a different prognosis. The authors found a higher prevalence of lacunar stroke subtype and of hypertension among patients with diabetes and they also observed that after correction for other risk factors and TOAST subtype, the association between diabetes and lacunar stroke remains statistically significant underlying how the relationship between diabetes and lacunar strokes could exist in diabetic subjects with ischemic stroke, partially independent from hypertension. This is an interesting finding in the light of several studies that have underlined the role of hypertension as the first risk factor for lacunar subtype [59,60] but this is actually true in patients without diabetes, whereas in diabetic ones hypertension could represent only a cofactor of lacunar stroke determinism [61]. Furthermore, Pinto et al. [62-70] with the purpose to evaluate the cerebrovascular morbidity both on a retrospective and a prospective evaluation in patients with diabetic foot in comparison to patients without diabetic foot complications showed a worse cerebrovascular risk profile in subjects with diabetes mellitus with diabetic foot compared to patients with diabetes mellitus without foot ulceration. They also observed a higher prevalence of both the lacunar and large artery atherosclerosis subtype with a slight higher prevalence of lacunar subtype in patients with diabetic foot suggesting the putative role of both microvascular disease and atherosclerosis in determining cerebrovascular morbidity in patients with diabetic foot. Finally, the stroke subtype which is mainly observed among patients with diabetes is the lacunar type, probably because diabetes may accelerate the atherosclerotic process both in intracranial that extracranial vessels contributing to the pathogenesis of lacunae consistent with the classical Fisher’s hypotesis of a hipoalinitic or athorothrombotic occlusion of the cerebral small vessels and therefore it is associated with a more insidious ischaemic damage to the brain, mainly manifesting as SVD and increased the risk of cognitive decline and dementia.

Discussion

Ischemic stroke is an important cause of morbidity and mortality worldwide and currently the leading cause of adult disability in developed countries. Several studies have shown a higher prevalence of ischemic stroke in subjects with diabetes mellitus. Among patients with diabetes several risk factors play a role together to promote the development of ischemic stroke. In the analysis of these risk factors can be identified diabetes-specific factors such as hyperglycemia and vascular risk factors such as hypertension and dyslipidemia [8-10]. In addition to these also genetic, demographic, and lifestyle factors contribute in varying degrees to the overall risk of people with diabetes [11-15]. As a whole, these factors, contribute to the characteristic atherogenic profile of the patients with diabetes mellitus, in which there is a complex interplay of several variables with inflammatory metabolic disorders and their effect on the cardiovascular system that may accelerate the atherosclerotic process both in intracranial that extracranial vessels. This could result in pathophysiological changes of cerebral vessels in people with diabetes and increase the risk of stroke. The SVD play an important role in the context of diabetic microangiopathy, in fact the subtype of stroke that is mainly found in the subjects with diabetes mellitus is the lacunar type. Thus, diabetes is associated with a more insidious ischemic damage to the brain, mainly manifesting as lacunar infarcts and thus increase the risk of dementia and lead to a steeper decline in cognitive function. On the other and the hyperglycemia play an important pathogenetic role in the acute phase of ischemic stroke as direct effect of neuronal damage and it is well known as a negative prognostic factor. Therefore, the interaction between diabetes and stroke is a bidirectional interaction and this underlines the close relationship between these two common diseases which often arise together. Finally the higher risk of stroke, especially lacunar type, that is observed in people with diabetes underline the importance of preventing the higher cerebrovascular risk which characterizes this class of patients with a multifactorial treatment of risk factors for stroke, in particular lifestyle factors, hypertension, and dyslipidemia with the aim to prevent a substantial number of these disabling strokes among patients with diabetes [8-15].

References


