ROLE OF DIABETES MELLITUS IN RECURRENT ISCHEMIC STROKES IN PATIENTS WITH ATRIAL FIBRILLATION

Gülçin Benbir Şenel, **Birsen İnce**

Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Neurology, Istanbul, Turkey

ABSTRACT

Objective: *Atrial fibrillation (AF) is an important risk factor for ischemic stroke, with a high morbidity and mortality ratios. Diabetes mellitus (DM) was reported as a strong and independent risk factor for both the occurrence of AF and ischemic stroke. In this context, here we investigated the influence of diabetes mellitus on the recurrence of ischemic stroke in patients with atrial fibrillation.*

Material and Method: *In this retrospective cohort study, we reviewed the files of 2798 patients with stroke followed in our cerebrovascular outpatient clinics for 15 years.*

Results: *A total of 313 patients (11.2%) with ischemic stroke had atrial fibrillation. Of these, 152 patients on regular follow-up were included; mean duration of follow-up was 94.6±52.2 (median, 34) months. The mean age of the study population was 70.0±10.3 years, and*

54.3% were females (83 patients). Diabetes mellitus was present in 28.3% (43 patients). The mean TTR (time in therapeutic range) calculated for INR was 56.6±35.5% (median, 58). Sixteen patients (10.5%) had a recurrent ischemic stroke. The presence of diabetes mellitus was very significantly associated with the re-occurrence of ischemic stroke in patients with AF (p=0.012), with an Odds ratio of 4.2 (1.4-12.7). TTR for serum fasting glucose levels was also significantly associated with recurrent ischemic stroke (p=0.011). TTR calculated for HbA1c (p=0.354) or for INR (p=0.106) did not show a significant association.

Conclusion: *The presence of diabetes mellitus and serum fasting glucose levels seems to be the most important and independent risk factors for recurrent ischemic stroke in patients with AF.*

Keywords: *Atrial fibrillation, ischemic stroke, diabetes mellitus.*

ATRİYAL FİBRİLASYONU OLAN HASTALARDA DİYABETİN İSKEMİK İNME REKÜRRENSİ ÜZERİNE ETKİSİ

ÖZET

Amaç: Atriyal fibrilasyon (AF) iskemik inme için önemli bir rik faktörüdür, yüksek morbidite ve mortalite oranlarına sahiptir. Diabetes mellitus (DM) hem AF'nin tetiklenmesinde hem de iskemik inme için bağımsız ve güçlü bir risk faktörüdür. Bu bağlamda, bu çalışmamızda, atriyal fibrilasyonu olan hastalarda diyabetin iskemik inme rekürrensi üzerindeki etkilerini araştırmayı hedefledik.

Materyal ve Metot: Bu retrospektif kohort çalışmasında, 15 yıl boyunca ayaktan inme polikliniğimizde takipte olan ardışık 2798 hasta dosyalarını inceledik.

Bulgular: Toplam 313 iskemik inme hastasında (%11,2) atriyal fibrilasyon mevcuttu. Bu hastalardan düzenli takiplere geldiği izlenen 152 hasta çalışmaya dahil edildi; ortalama takip süresi 94,6±52,2 (ortanca, 34) ay idi. Çalışma grubunun ortalama yaşı 70,0±10,3 yıl olarak hesaplandı, %54,3'ü kadındı (83 hasta). Diabetes mellitus hastaların %28,3'ünde (43 hasta) mevcuttu. INR değerleri için ortalama TTR (time in therapeutic range) %56,6±35,5 (ortanca, %58) olarak hesaplandı. On altı hastada (%10,5) tekrarlayıcı inme izlendi. Diabetes mellitus varlığı ile inme tekrarı arasında oldukça yüksek anlamlı ilişki saptandı (*p*=0,012), Odds oranı 4,2 (1,4-12,7) idi. Serum açlık glukoz düzeyleri için hesaplanan TTR değerlerinin de iskemik inme tekrarı ile anlamlı ilişkili olduğu gözlendi (*p*=0,011). HbA1c için (*p*=0,354) veya INR için (*p*=0,106) hesaplanan TTR değerleri ile iskemik inme tekrarı arasında anlamlı ilişki saptanmadı.

Sonuç: Diabetes mellitusun varlığı ve serum açlık glukoz düzeyleri, atriyal fibrilasyonu olan hastalarda inme tekrarı için en önemli ve bağımsız risk faktörleridir.

Anahtar kelimeler: Atriyal fibrilasyon, iskemik inme, diabetes mellitus.

INTRODUCTION

Atriyal fibrillation (AF) is an important risk factor for ischemic stroke, with an increased risk by 4 to 5 fold.[1] Patients with highly symptomatic AF are at particular risk for higher morbidity and mortality, and several measures of AF chronicity and severity are significantly predictive of poor prognosis due to cardiovascular complications.[2] Moreover, the presence of AF also constitute an important correlate of recurrent strokes, for which stroke risk stratification schemes have been developed and validated to facilitate the decision of whether to prescribe long-term anticoagulation. Leading clinical practice guidelines[3,4] recommend a risk-based approach to the decision of anticoagulation in AF, such as CHADS2,[5] CHA2DS2-VASc[6] or the ATRIA stroke risk scores.[7] In the original validation cohort for CHA2DS2-VASc score from Denmark, the highest relative ischemic stroke risk was conferred by the presence of diabetes mellitus (Hazard ratio, HR: 4.46), followed by advanced age (65–75 years, HR:3.68), hypertension (HR: 2.76), heart failure (HR: 1.92), female sex (HR: 1.60), and vascular disease (HR: 0.97).[6]

Diabetes mellitus (DM) is well-known as a strong and independent risk factor for both the occurrence of AF and ischemic stroke, with an odds ratio (OR) of 2.13 and 1.86 respectively.[7-9] The risk of AF and stroke was shown to increase with the duration of DM, high HbA1c levels, and poor blood glucose control.[10,11] Diabetes mellitus was also associated with an increased stroke severity, poorer functional recovery, and higher mortality.[12-14] Because diabetes mellitus has been associated with worse long-term vascular prognosis,[15] special attention should be paid to the patients with diabetes after stroke. Here we investigated the influence of diabetes mellitus on the recurrence of ischemic stroke in patients with atrial fibrillation.

MATERIALS AND METHODS

In this retrospective cohort study, we reviewed the files of 2798 patients with stroke followed in our cerebrovascular outpatient clinics between June 1996 and June 2014. Of these, 313 patients (11.2%) with ischemic stroke had atrial fibrillation. We could reach 152 of these patients and questioned the presence of recurrent ischemic stroke. TOAST classification was used in the determination of the subtype of the ischemic strokes, as atherothrombotic, cardioembolic, small vessel disease, other rare etiologies and stroke of undetermined etiology.[16] The mean follow-up period was for a mean period of 94.6+52.2 (median, 34) months.

Demographic data and the risk factors were reviewed in these 152 patients. Risk factors included gender, age, comorbid carotid atherosclerosis, nature of AF (persistent or paroxysmal), coronary artery disease, ventricular dysfunction (ejection fraction <50%),

non-insulin dependent diabetes (fasting blood glucose ≥7.8 mmol/L in two consequent measurements or blood glucose level of ≥11.1 mmol/L after 75 mg oral glucose tolerance test), antidiabetic therapy, the presence of hypertension (HT; systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg that was recorded in medical files, or the use of antihypertensive therapy), course of HT (regulated or not), dyslipidemia (blood total cholesterol ≥200 mg/dl, triglyceride ≥150 mg/dl, LDL cholesterol ≥100 mg/dL, HDL cholesterol ≤40 mg/dL, or the use of lipid-lowering therapy), use of anti-thrombotic or anticoagulation therapy, smoking status, and alcohol intake.

Detailed data was collected on medical history including oral anticoagulation use, and international normalized ratio (INR) data; the time in therapeutic range (TTR) was calculated based on the Rosendaal method.[17] Therapeutic range for diabetes mellitus was similarly quantified on the basis of serum fasting glucose and HbA1c measurements.

The statistical analyses were performed with the software (version 15.0 for Windows; SPSS, Chicago, IL). The data was given as mean ± standard deviation or in percentages, appropriately. In the analysis of nominal variables, Pearson chi-square test was used, Mann-Whitney U test was used for independent numerical variables which did not normally distributed. A p value of ≤0.05 was considered statistically significant.

RESULTS

The mean age of the study population was 70.0±10.3 years, and 54.3% of them were females (83 patients). Comorbid atherosclerosis was present in 36 patients (23.6%). AF was persistent in 68.4% and paroxysmal in 29.3% of the patients. While 53.7% of them had no anti-arrhythmic use, 21.1% were on a beta-blocker agent, 15.0% had digoxin glycosides, 3.4% had a calcium channel blocker, and 2.7% had amiodarone therapy. Surgical pacemaker was implanted in 4.1% of the patients. Coronary artery disease was present in 30.9% (47 patients) of the patients. Ventricular dysfunction was present in 42.1%; the mean EF was calculated as 53.8±7.4; ranging between 35 and 70%. Diabetes mellitus was present in 28.3% (43 patients); most of them were on oral anti-diabetic therapy (51.2%). Hypertension was present in 79.6% of the patients and only 66.4% were strictly regulated. Dyslipidemia was present in 32.9%, smoking was present in 27.6% and alcohol intake was observed in only 7.9% of the study population.

Table 1. Comparison of demographic and clinical data in study population.

Variables	Patients without recurrent stroke (n=136)	Patients with recurrent stroke (n=16)	*p* value
Mean age (years)	69.9±19.6	66.6±10.7	0.202
Female gender (%)	53.6	43.7	0.224
Comorbid atherosclerosis (%)	22.1	18.8	0.569
Coronary artery disease (%)	31.6	37.5	0.192
Atrial fibrillation (%)	70.5	62.5	0.399
Ventricular dysfunction (%)	58.8	68.7	0.474
Mean ejection fraction (%)	53.6±7.9	56.6±2.8	0.593
Hypertension (%)	77.2	93.7	0.127
Diabetes mellitus (%)	19.1	37.5	0.012
Strictly-regulated hypertension (%)	93.4	75.0	0.081
Hyperlipidemia (%)	31.6	31.2	0.563
Smoking (%)	27.2	31.2	0.431
Alcohol intake (%)	9.5	6,2	0.234
Mean TTR for INR (%)	59.2±35.4 (median, 64)	34.7±35.1 (median, 50)	0.106
Mean TTR for glucose (%)	73.3±44.1 (median, 71.4)	20.1±27.8 (median, 25)	0.011
Mean TTR for HbA1c (%)	62.5±51.8 (median, 60)	30.0±44.7 (median, 40)	0.354

TTR: Time in Therapeutic Range, **INR:** International Normalized Ratio.

TOAST classification revealed that 90.8% of the patients had cardioembolic stroke, 3.3% had atherothrombotic stroke (5 patients), 3.3% had stroke due to small vessel disease (5 patients), 2.0% had dissection (3 patients) and one patient (0.7%) had an underlying hematological abnormality. While 2 patients had no anti-coagulation or anti-aggregant therapy (because of hemorrhagic complications), 50% of the population had anti-coagulation therapy (76 patients), 31.6% had anti- aggregant therapy (48 patients), and 17.1% of them had dual anti- aggregant therapies (26 patients). The mean TTR calculated for INR was found as 56.6±35.5% (median 58%), ranging between 0-100%. After a mean follow-up of 94.6±52.2 (median, 34) months, 16 patients (10.5%) had a recurrent ischemic stroke.

In the analysis of prognostic factors, we found that age (*p*=0.202), gender (*p*=0.224), comorbid atherosclerosis (*p*=0.569), type of AF (*p*=0.399), ventricular dysfunction (*p*=0.474), mean EF values (*p*=0.593), hypertension (*p*=0.127), hyperlipidemia (*p*=0.563), smoking (*p*=0.431), and alcohol intake (*p*=0.234) were not found to be associated with the occurrence of recurrent ischemic stroke (see Table 1). Whether HT was strictly regulated or not showed a

Table 2. Comparison of demographic and clinical data in patients with and without diabetes mellitus (DM).

Variables	Patients without DM (n=109)	Patients with DM (n=43)	p value
Mean age (years)	70.2±10.5	69.4±9.8	0.558
Female gender (%)	52.8	58.1	0.340
Comorbid atherosclerosis (%)	23.1	26.2	0.423
Coronary artery disease (%)	29.4	32.6	0.368
Persistent / Paroxysmal atrial fibrillation (%)	73.6 / 26.4	63.4 / 36.6	0.155
Ventricular dysfunction (%)	55.8	72.4	0.090
Mean ejection fraction (%)	53.9±7.7	53.6±7.0	0.992
Hypertension (%)	72.5	97.7	<0.001
Strictly-regulated hypertension (%)	65.1	67.4	0.591
Hyperlipidemia (%)	30.3	39.5	0.183
Smoking (%)	27.5	27.9	0.556
Alcohol intake (%)	9.2	4.7	0.286
Mean TTR for INR (%)	60.7±33.5 (median, 66)	38.2±39.5 (median, 33)	0.036

TTR: Time in Therapeutic Range, **INR:** International Normalized Ratio.

borderline significance in association with recurrent ischemic stroke (*p*=0.081). The presence of diabetes mellitus, however, was very significantly associated with the re-occurrence of ischemic stroke in this group of patients with AF (*p*=0.012), with an Odds ratio of 4.2 (1.4-12.7). TTR for serum fasting glucose levels was also significantly associated with recurrent ischemic stroke (*p*=0.011), while TTR calculated for HbA1c (*p*=0.354) or for INR (*p*=0.106) did not show a significant association.

The analysis of the variables on the basis of the presence of DM is given in Table 2. Only the presence of HT was significantly more common in patients with DM (*p*<0.001), while other risk factors associated with stroke were similar between two groups. TTR calculated for INR was also found to be worse in patients with diabetes (*p*=0.036). The mean TTR calculated for serum fasting glucose was 52.7±47.1% (median 66%; between 0-100), and the mean TTR calculated for HbA1c was 46.4±49.8 (median 50%; between 0-100%). The subtypes of stroke were not significantly different between two groups (*p*=0.090).

In patients without diabetes, the only significant variable associated with recurrent ischemic stroke was the TTR calculated for INR (*p*=0.021), while all other variables failed to show a significant association. Whether HT was strictly-regulated or not was close to be significantly associated with the recurrent ischemic stroke (*p*=0.075). In patients with DM, on the other hand, TTR calculated for INR was no longer significantly associated with the recurrent ischemic

stroke (*p*=0.485), while TTR calculated for serum fasting glucose levels (*p*=0.011) was significantly associated. All other variables failed to have a significant association with the recurrent ischemic stroke. The comorbid presence of both DM and HT was also significantly associated with higher ratios of recurrent ischemic stroke (*p*=0.009), with an Odds ratio of 4.4 (1.4-13.3). The presence of DM and female gender, however, did not show a significant association (*p*=0.345), neither the presence of DM and age ≥75 years (*p*=0.300).

DISCUSSION

Diabetes mellitus is known to be significantly associated with poorer outcome in patients with stroke.[9] A large number of studies has demonstrated a worse functional outcome, along with higher long-term mortality in stroke patients with diabetes.[12,18] The ADVANCE study showed that the mortality in DM patients was higher in the presence of AF.[10] In the presented study, we studied patients with stroke and atrial fibrillation, and demonstrated that the Odds ratio for recurrent ischemic stroke was four times higher in the presence of DM. This may suggest that DM may be the most important risk factor for recurrent ischemic stroke in patients with AF.

Age and female sex have been reported as important and consistent predictors of stroke and mortality in patients with AF.[19-22] In this context, age and female gender constitute items in CHA2DS2-VASc risk stratification scheme designed for AF patients. However, we did not find a significant association between gender and recurrent ischemic stroke in patients with AF and DM. Similar results were also reported in the literature.[23] In addition, gender was not associated with recurrent ischemic stroke in our patients with AF, and those with or without DM. Similarly, Euro Heart Survey[21] did not observe any effect of gender on the risk of all-cause mortality, either. Concomitant risk factors placed in CHA2DS2-VASc risk score may explain this difference in the literature.

AF chronicity and ventricular dysfunction was demonstrated to significantly be associated with several cardiovascular and noncardiovascular comorbidities.[2] The Euro Heart Survey showed higher rates of thromboembolic events in patients with permanent AF.[21] The ACTIVE W study, on the other hand, showed that the risk of thromboembolic events did not differ between paroxysmal and permanent AF.[23] Similarly in our study population, we failed to show a significant association between the type of AF, as well as the presence of ventricular dysfunction and

lower EF values, with recurrent ischemic stroke. It was suggested that not only the type of AF, but the duration and frequency of paroxysmal AF may be related with the occurrence of thromboembolic risk.[24]

The prevalence of HT was very high in our patients with DM in compared to those without. Although HT itself was not found to play an important role in recurrent ischemic stroke in our study population, the comorbidity of HT and DM was significantly associated with recurrent ischemic stroke in patients with AF, which proved a small but significant risk for the recurrent ischemic stroke in additional to DM alone. It was hypothesized in the SPS3 trial[25] that lower targets for systolic blood pressure would be particularly beneficial in the prevention of recurrent strokes among patients with DM, but this was not confirmed yet.

In our study, INR regulation calculated as TTR was the only significant risk factor for the recurrent ischemic stroke in patients without DM. Furthermore, the serum fasting glucose levels were the only significant associate for the recurrent ischemic stroke in patients with DM. Moreover, although TTR for INR was not significantly associated with the recurrent ischemic stroke in patients with DM, it was significantly lower in the patients with DM. Nevertheless, better management of patient with AF – especially in the absence of DM as another risk factor for stroke – may require novel anti-coagulant therapies, for which the long term prognostic results should be demonstrated. In stroke patients with AF and DM, on the other hand, glycemic control was found to be the most important factor associated with recurrent ischemic stroke. In the literature, although hyperglycemia and poor outcome following stroke have been demonstrated in many studies,[26,27] there is only one study[28] showing that HbA1c levels were associated with the prognosis of stroke in patients with DM. In our study population with ischemic stroke and AF, we failed to show a significant association with HbA1c levels, but demonstrated a strong association between the presence of DM and serum fasting glucose levels with the recurrent ischemic stroke.

Multiple observational studies have demonstrated greater stroke severity and greater functional impairment in the patients with hyperglycaemia. Acute glucose excursion has been shown to trigger oxidative stress and endothelial dysfunction, while chronic hyperglycemia was also accused of poor outcome in stroke patients with diabetes, which alters microvascular hemodynamics and membrane function, reduces cerebral blood flow, and impairs oxygen exchange.[29] Moreover, DM was reported to be associated not only with stroke but also with AF; a longer duration of DM and worse glycemic control has been independently associated with increased risk of AF.[30,31]

Among limitations of our study, we did not analyze the hemorrhagic complications of anti-coagulant or anti-aggregant therapy; however, this was beyond the scope of this study. The investigation of DM-related factors in a subgroup of patients with TTR for INR higher than 90% may better reveal the effects of confounding factors. Another main issue of the study population is the low numbers of patients with diabetes mellitus. Although the influences of DM is well-documented in patients with ischemic stroke, especially of atherothrombotic type or in small vessel disease, the deleterious effects of DM in stroke patients with AF should be confirmed in larger studies with prospective and longitudinal design.

CONCLUSION

On these bases, we may conclude that in a stroke patient with AF, the most important risk factor for recurrent ischemic stroke may be diabetes mellitus with poor glycemic control; which has deleterious effects on both ischemic brain tissue and atrial fibrillation. For this reason, the presence of DM should particularly be searched and vigorously be treated in patients with ischemic stroke and atrial fibrillation.

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