ASSOCIATION OF DYSLIPIDEMIA AS A RISK FACTOR FOR THE FIRST EPISODE OF ISCHEMIC STROKE

Muhammad Abdur Rahman Afridi, Farah Rabbani, Yasmin Akhtar

Department of Medicine, Lady Reading Hospital Peshawar

Address for correspondence:
Muhammad Abdur Rahman Afridi
Department of Medicine, Lady Reading Hospital Peshawar

E-mail:
rahmanafridi@hotmail.com

Date Received:
22nd September, 2022
Date Revised:
15th March, 2023
Date Accepted:
18th April, 2023

ABSTRACT

Objective: To determine the frequency and association of dyslipidemia in patients with the first episode of ischemic stroke.

Methodology: This observational, descriptive study of 126 patients of the first episode of ischemic stroke was conducted in the Medicine department of Lady Reading Hospital Peshawar from August 2020 to March 2021. After approval of the study by the hospital's Ethical Review Board, patients were enrolled by non-probability consecutive sampling technique. Relevant investigations of the patients were carried out, including fasting serum lipids and brain scan/MRI. SPSS® version 21 was used for data entry and statistical analysis; a Chi-square p-value ≤0.05 was considered significant.

Results: A total of 126 patients, 70(55.6%) men and 56(44.4%) women with the first-ever ischemic stroke, had a mean age of 54.56 years ±9.74SD. Dyslipidemia was found in 51.6% of patients; 53.8% of men and 46.2% of women, however, the gender difference was insignificant (X^2 (df1)=0.159, p=0.690). Among 51.6% of patients with dyslipidemia, hypercholesterolemia was the most common abnormality in 29.4% while raised levels of Low-density lipoproteins-cholesterol (LDL-C) were seen in 7.1% of patients. No significant difference in dyslipidemia was observed in different age groups (X^2 (df3)=2.263, p=0.520). Gender-wise, ischemic stroke occurred significantly in the younger men compared to women (X^2 (df3)=8.762, p=0.033).

Conclusion: The present study concludes that dyslipidemia was not significantly associated with patients with the first episode of ischemic stroke. Ischemic stroke occurred more significantly in younger men compared to women; however, both genders were equally affected in older age.

Keywords: Ischemic Stroke; Dyslipidemia; Cholesterol; Cerebral Infarction; Stroke Risk Factors

INTRODUCTION

Stroke, commonly known as cerebrovascular accident (CVA), is "a focal neurological deficit (hemiparesis/hemiplegia/cranial nerve palsy/dysphasia) of sudden onset and lasting longer than 24 hours, of vascular origin, with neuroimaging evidence of brain tissue infarction or hemorrhage".[1] Globally, stroke and cardiovascular diseases are major health problems and carry a huge socioeconomic burden.[2] It is a common cause of death and disability, particularly in middle- and low-income countries.[3] "The American Heart Association (AHA)-Stroke-2016 Updates" reported that 87% of strokes are ischemic, 10% hemorrhagic and 3% are subarachnoid hemorrhage.[2,4] Stroke is a heterogeneous disease of cerebrovascular origin with multifactorial risk factors; some of the factors are modifiable and treatable like hypertension, Diabetes Mellitus (DM), smoking, and dyslipidemia while others are fixed and non-modifiable like age, gender, and ethnicity. It implies that stroke is a preventable disease.[5]

A decrease in the stroke incidence was seen in the developed world by following strict prevention and control of risk factors whereas it is rising in the developing world due to lifestyle changes and westernization. A decline in the incidence of stroke was also seen in the United States in 2013. This was achieved through control measures of cardiovascular risk factors and control of hypertension, DM, dyslipidemia, and smoking cessation. This ultimately contributed to the decrease in stroke mortality.[2]

Many studies reported conflicting findings regarding the association of cholesterol with stroke. "The Honolulu Heart Program" data revealed that elderly Japanese men with decreased levels of high-density lipoprotein-cholesterol (HDL-C) were more at risk of future thromboembolic stroke whereas a meta-analysis in the "Asia Pacific Region" revealed no association between risk of stroke and low HDL-C levels.[2] A study from Finland of 58,235 participants followed for ischemic stroke for more than 20 years found an in-

This article may be cited as
Afridi MAR, Rabbani F, Akhtar Y. Association of dyslipidemia as a risk factor for the first episode of ischemic stroke. J Postgrad Med Inst 2023;37(2): 119-124. http://doi.org/10.54079/jpmi.37.2.3174

verse relationship of HDL-C with the risk of stroke, especially in women.[2] A cohort study of 267500 Chinese found a positive association between Triglyceride, LDL-Cholesterol, total cholesterol, and ischemic stroke and a negative association between HDL-C and ischemic-stroke.[6] Khan et al in a review of seven studies from various parts of Pakistan revealed dyslipidemia prevalence of 9.9% to 32% among patients with stroke.[7]

Although epidemiological studies failed to establish the role of lipids as a risk factor for ischemic stroke; however, clinical trials have shown promising results of statins in reducing ischemic stroke. Patients in "the Physicians' Health Study" with the hyperlipidemia had a higher risk of stroke.[4] Statins use reduces the risk of ischemic stroke but also increases the chances of hemorrhagic stroke.[8] As the results of the earlier research regarding dyslipidemia in ischemic stroke in different regions were variable and inconsistent so we planned this study to determine the frequency and association of dyslipidemia in patients presenting for the first time with ischemic stroke to our tertiary care hospital. The study results will not only be a valuable addition to the local data on the subject but will also be helpful in the identification of potentially high-risk patients and their subsequent management as well. This will help prevent the devastating disease of ischemic stroke and reduce the overall socioeconomic burden on the family and healthcare sector as well.

METHODOLOGY

This descriptive observational study was done in the Department of Medicine, Lady Reading Hospital Peshawar, from August 2020 to March 2021. A total of 126 patients presenting with the first episode of ischemic stroke were selected by non-probability consecutive sampling technique. The sample size of 126 was estimated with a 95% confidence interval, 5% margin of error, and a frequency of dyslipidemia of 9%[7] in patients of ischemic stroke, by WHO sample size estimation software.

This study includes all patients of both genders aged 20 years and above, who have been diagnosed with a first episode of ischemic stroke on neuroimaging. To minimize bias in the study results, patients with certain medical conditions or behaviors that could potentially confound the results were excluded. These include patients with diabetes mellitus (DM), those currently taking statin therapy, those with acute coronary syndrome, those who have previously had a stroke, epilepsy, or hypertension, and those who are actively smoking.

The presence of dyslipidemia was determined based on blood samples taken in the laboratory after an overnight fast of 8 hours. Dyslipidemia was defined as having hypercholesterolemia (serum cholesterol level greater than 200 mg/dL), hypertriglyceridemia (serum triglyceride level greater than 150 mg/dL), increased LDL-C (serum LDL-C level greater than 130 mg/dL), or decreased HDL-C (serum HDL level less than 35 mg/dL). Ischemic stroke was defined as the sudden onset of focal neurological symptoms and/or signs, such as hemiparesis, hemiplegia, cranial nerve palsy, or dysphasia, lasting longer than 24 hours, and of vascular origin, with neuroimaging evidence of brain tissue infarction.

After the approval of the study by the institution's Ethical Review Board, the study details were explained to the patient's attendants and written informed consent was obtained. The patient's history was obtained and a physical examination with special emphasis on neurological dysfunction was performed. Relevant investigations like blood sugar and fasting lipid profile were done in the hospital laboratory. All information obtained from laboratory reports and demographic data was recorded in a predesigned proforma. The data were analyzed using IBM® SPSS® Statistics version 21. Mean ± standard deviations (SD) were calculated for quantitative variables like age, cholesterol, triglycerides, HDL-C, and LDL-C. Frequencies and percentages for categorical variables like gender, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, increased LDL-C & decreased HDL-C calculated. Dyslipidaemia was stratified among age and gender to see the effect modifications. Chi-square p-value≤0.05 was considered significant.

RESULTS

Among 126 patients with the first-ever ischemic stroke, 70(55.6%) were men and 56(44.4%) were women, as shown in Table1. The age range was 30 to 70 years with a mean age of 54.56 years ±9.74 SD. Lipids-related statistics are shown in Table 2. Among 51.6% of patients with dyslipidemia, hypercholesterolemia was the most common abnormality in 29.4% while raised LDL-C levels were seen in 7.1% of patients. The gender distribution in different age groups of the patients revealed that ischemic stroke occurred in younger men compared to women (X^2(df3)=8.762, p=0.033), as shown in Table 3. However, both genders were equally affected in older age. Dyslipidemia was found in 51.6% of patients; 53.8% of men and 46.2% of women, however, the difference was insignificant (x^2(df1)=0.159, p=0.690), as shown in Table 4. Analysis of dyslipidemia with different age groups was also statistically insignificant (x^2(df3)=2.263, p=0.520).

DISCUSSION

Our study findings are similar to another recent study by Khan et al[9] from Lahore which reported the mean age of stroke patients as 53.09±12.51 years with 57.7% men, but a comparatively low frequency (39.42%) of dyslipidemia. Similarly, Kumar et

Table 1: Demographic Characteristics of Ischemic Stroke patients (n=126)

Variables		Frequency	Percentage
Gender	Male	70	55.6
	Female	56	44.4
Age groups	30 to 40 years	13	10.3
	41 to 50 years	25	19.8
	51 to 60 years	51	40.5
	61 to 70 years	37	29.4
Lipids profile	Dyslipidemia Present	65	51.6
	Hypercholesterolemia	37	29.4
	Hypertriglyceridemia	10	7.9
	Raised LDL-C* levels	09	7.1
	Low HDL-C* levels	23	18.3

LDL-C* low-density lipoprotein-cholesterol HDL-C* high-density lipoprotein-cholesterol

Table 2: Descriptive Statistics of Ischemic Stroke patients (n=126)

Variables	Minimum	Maximum	Mean	Std. Deviation
Age in years	30	70	54.563	9.7419
Total cholesterol (mg/dL)	132.0	502.0	176.349	38.1492
Triglycerides (mg/dL)	110.0	351.0	136.413	21.4563
HDL-C (mg/dL)	21.0	58.0	45.040	9.8634
LDL-C (mg/dL)	118.0	138.0	124.524	3.9022

Table 3: Gender-wise Age group Distribution of Ischemic Stroke patients (n=126)

Gender	Age groups				Total
	30 to 40 years	41 to 50 years	51 to 60 years	61 to 70 years	
Male	08(11.4%)	20(28.6%)	23(32.9%)	19(27.1%)	70(55.56%)
Female	05(8.9%)	05(8.9%)	28(50.0%)	18((32.1%)	56(44.44%)
Total	13(10.3%)	25(19.8%)	51(40.5%)	37(29.4%)	126(100%)

Pearson Chi-Square(X2)=8.762, (df=3), p=0.033

Table 4: Dyslipidemia and Gender Distribution of ischemic Stroke patients (n=126)

Dyslipidemia	Gender		Total
	Male	Female	
Present	35(53.8%)	30(46.2%)	65(51.59%)
Absent	35(57.4%)	26(42.6%)	61(48.41%)
Total	70(55.6%)	56(44.4%)	126(100%)

Pearson Chi-Square(x2)=0.159, df=1, p=0.690

al[10] reported from Jamshoro, a mean age of 59.72±6.40 years with 76% of men. Abid et al[11] from Multan also reported mean age as 55.96±15.76 years with 52% women and a comparatively lower prevalence of 37.1% dyslipidemia. Aslam et al[12], on the other hand, reported comparatively young patients of stroke with a mean age of 39.29±11.82 years with the majority (52.4%) of women. The gender distribution of our present study results is comparable to a Chinese study which reported 60.5% of men with stroke [13]. Contrary to the present study, our previous study[14] on stroke was dominated by males (68%) and 32% were females; patients were comparatively older and had a mean age of 63.44±13.85 years; 24% of whom had hyperlipidemia. The NOMAS cohort study also reported mean age of 68.8 years with a majority (63.5%) of females; higher LDL-C levels were associated with a higher risk of cerebral infarction.[5] In the present study, 51.6% of the patients had dyslipidemia, which is comparable to another study finding of 55% from Faisalabad[15], Pakistan.

Different frequency figures regarding dyslipidemia in stroke patients have been reported in various studies. Khan et al [16] from Peshawar reported the lowest frequency of 3.3% dyslipidemia and 19.65% by Sheikh et al [17] from Karachi. A review of seven studies from various parts of Pakistan reported dyslipidemia between 9.9 to 32% in stroke.[7] Around 19% of dyslipidemia was reported in ischemic stroke patients in Islamabad[18], 30% in Jamshoro, Sind[10], and 37.1% in Multan.[11] Similarly, 65.7% of dyslipidemia was found in South-Indian patients.[19] The World Health Organization (WHO), on the other hand, reported 30.3% dyslipidemia prevalence in Southeast Asia.[5] Dyslipidemia in our present study of 51.6% is higher in contrast with our previous study[14] findings of 24%. The likely explanation for the discrepancy between our present study results with that of the earlier findings is the difference between sample selection and inclusion criteria; all types of stroke patients with multiple risk factors and comorbidities were included in the previous study while the current study included patients of ischemic stroke and dyslipidemia only, and no other comorbidity. Other reasons for variations in the results of other studies include differences in the sample size of the studies, inclusion/exclusion criteria in the sample selection and comorbidities, types of stroke, ethnicity, and lifestyle including dietary habits of patients in different regions, and so on.

Varbo et al from the "Copenhagen City Heart Study"[20] consisting of 6,372 men and 7,579 women followed for 33 years showed that hypertriglyceridemia was associated with increased risk of stroke, particularly in women, whereas both hypertriglyceridemia and hypercholesterolemia were associated

with increased risk of stroke in men. The multicenter INTERSTROKE study[3] of 26919 participants with 10388 ischemic stroke patients from 32 countries revealed that Apolipoproteins were significantly associated with ischemic strokes. Similarly, "The Helsinki Young Stroke Registry" reported dyslipidemia as a risk factor in 60% of stroke patients.[21] "The Asia Pacific cohort studies collaboration"[22] reported that each 1mmol/L increase in cholesterol increases the risk of ischemic stroke by 25%. Low HDL-C and high LDL-C levels are associated with a higher risk whereas the role of high Triglycerides is less clear.[8] Aslam et al [12] also found that high VLDL-C, low HDL-C, and high Triglycerides had a significant association with the category of stroke. A protective role of HDL-C in ischemic stroke has been reported in case-control studies, like "Systolic Hypertension in the Elderly Program (SHEP)", and "Prospective Cohorts of Japanese men and women".[5] Tsivgoulis[23] in a special review reported that high cholesterol levels predispose to ischemic stroke and low levels to cerebral hemorrhage. Controlling modifiable risk factors can significantly reduce stroke. Contrary to this, a large cohort of 14000 middle-aged participants followed up for 10 years found no consistent association between ischemic stroke and LDL-C.[24] Conversely, the "Cardiovascular Health Study-(CHS)" and the "Atherosclerosis Risk in Communities Study-ARICS" showed no association between ischemic stroke and LDL-C or HDL-C levels.[5,24]

As evident from the above discussion, epidemiological studies have shown conflicting results on dyslipidemia as a predictor of ischemic stroke. It may not have a role in the pathogenesis of some subtypes of ischemic strokes, like cardio-embolic and lacunar infarcts.[8] Hyperlipidemia causes atherosclerosis predisposing to athero-thrombotic/cardio-embolic ischemic stroke.[25] Reducing LDL-C by 1mmol/L reduces the stroke risk by 21.1% as revealed in a meta-analysis.[26] Statins use reduces the risk of vascular events including ischemic stroke but also increases the chances of hemorrhagic stroke.[8] Epidemiological and observational studies revealed a complex relationship between stroke and lipids. The association depends not only on the subtypes of stroke but also on the lipids components as well. Dyslipidemia is strongly associated with atherosclerotic types of ischemic stroke; however, lower levels of cholesterol were correlated with a higher risk of hemorrhagic stroke. Similarly, total cholesterol and LDL-C were strongly associated with a higher incidence of ischemic stroke. An inverse relationship was found between stroke and HDL-C levels.[27]

CVA is a multifactorial and heterogeneous disease with different subtypes; probably that is why associating different risk factors yielded conflicting results. For instance, lacunar infarcts due to small perforating vessels are primarily related to DM and high blood pressure; the cardio-embolic stroke is related to intra-cardiac clot formation, whereas atherosclerosis-related ischemic stroke is influenced by dyslipidemias. Therefore, subtype categorization of the stroke is not ideal and can result in an underestimation of the effect of a risk factor.[5]

Public health implications: The present study has important public health implications. There is a dire need to understand exactly which risk factor(s) need management. This 'targeted approach' to a particular risk factor will not only simplify the treatment options but will be cost-effective as well. Furthermore, it will be helpful in the prevention of the occurrence and recurrence of ischemic stroke.

Study Limitations: The present study was a single-center, tertiary care hospital-based study, and hence its results findings cannot be generalizable to patients in the community; especially patients in remote rural areas of the province, having inadequate and limited access to the health facility. Therefore large-scale or multi-center studies are needed at the basic healthcare/community level to draw the actual picture of the problem.

CONCLUSION

The present study concludes that dyslipidemia was not significantly associated with the first-ever episode of ischemic stroke. Ischemic stroke occurred more significantly in younger men than women; however, there was no significant gender difference in the older age.

REFERENCES

1. Shiber JR, Fontane E, Adewale A. Stroke registry: hemorrhagic vs ischemic strokes. Am J Emerg Med. 2010;28(3):331-3. DOI:10.1016/j.ajem.2008.10.026.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38-360. DOI: 10.1161/CIR.0000000000000350.
3. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761-75. DOI:10.1016/S0140-6736(16)30506-2.
4. Bowman TS, Sesso HD, Ma J, Kurth T, Kase CS, Stampfer MJ, et al. Cholesterol and the risk of ischemic stroke. Stroke. 2003;34(12):2930-4. DOI:10.1161/01.STR.0000102171.91292.DC.
5. Willey JZ, Xu Q, Boden Albala B, Paik MC, Moon YP, Sacco RL, et al. Lipid profile components and risk of ischemic stroke: the Northern Manhattan Study (NOMAS). Arch Neurol.

2009;66(11):1400-6. DOI:10.1001/archneurol.2009.210.
6. Gu X, Li Y, Chen S, Yang X, Liu F, Li Y, et al. Association of Lipids With Ischemic and Hemorrhagic Stroke: A Prospective Cohort Study Among 267 500 Chinese. Stroke. 2019;50(12):3376-84. DOI:10.1161/STROKEAHA.119.026402.
7. Khan FS, Zafar A, Malik A. Stroke In Pakistan: Reality, Challenges And A Call For Action. Pak J Neurol Sci. 2008;3(1):14–9.
8. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Dyslipidemia as a risk factor for ischemic stroke. Curr Top Med Chem. 2009;9(14):1291-7. DOI:10.2174/156802609789869628.
9. Khan RSU, Nawaz M, Khan S, Raza HA, Nazir T, Anwar MS, et al. Prevalence of Dyslipidemia in Ischemic Stroke Patients: A Single-Center Prospective Study From Pakistan. Cureus. 2022;14(6):e25880. DOI:10.7759/cureus.25880.
10. Kumar R, Shah MI, Lakhair MA, Memon Z. Ischemic stroke; frequency of dyslipidemia and other risk factors at Tertiary Care hospital Hyderabad/ Jamshoro. Prof Med J. 2016;23(8):925-31. DOI: 10.17957/TPMJ/16.3385.
11. Abid N, Khan SA, Taseer I. Frequency of Hyperlipidemia in Patients Presenting with Ischemic Stroke. Pak J Med Health Sci. 2012; 6(2):423-7.
12. Aslam MS, Nasir KM, Hussain H, Saeed M, Walayt MS, Ahmad W, et al. Pattern of Dyslipidemias and their Association with Ischemic and Hemorrhagic Stroke. J Islamabad Med Dent Coll. 2017;6(3):135-40.
13. Yao XY, Lin Y, Geng JL, Sun YM, Chen Y, Shi GW, et al. Age- and gender-specific prevalence of risk factors in patients with first-ever ischemic stroke in china. Stroke Res Treat. 2012;2012:136398. DOI:10.1155/2012/136398.
14. Afridi M, Ali Z, Muhammad R, Ahmad A, Alam I. Age and gender specific stroke risk factors in a teaching hospital in Khyber Pakhtunkhwa. J Postgrad Med Inst. 2015;29(2):76-82.
15. Gul MM, Ali W, Iqbal S, Bano M, Memon A, Hussain W. Frequency of dyslipidemia in patients presented with ischemic stroke. Pak J Med Health Sci. 2021;35(34):1212–3.
16. Khan H, Khattak MI, Zarif M. Principal causes of coma in medical units of a tertiary care hospital of Peshawar. J Postgrad Med Inst. 2008;22:201-4.
17. Shaikh NA, Bhatty S, Irfan M, Khatri G, Vaswani AS, Jakhrani N. Frequency, characteristics and risk factors of carotid artery stenosis in ischaemic stroke patients at Civil Hospital Karachi. J Pak Med Assoc. 2010;60(1):8-12.
18. Baluch UT, Kiani I, Badshah M. Association of dyslipidemia and ischemic stroke. Ann Pak Inst Med Sci. 2008;4(3):165-7.
19. Subburaj T, Kumarasamy S, Velayudam S. Etiology and risk factors among young patients presenting with stroke in a tertiary care hospital in South India. Int J Res Med Sci. 2017;5:1027-32. DOI:10.18203/2320-6012.ijrms20170656.
20. Varbo A, Nordestgaard BG, Tybjaerg Hansen A, Schnohr P, Jensen GB, Benn M. Nonfasting triglycerides, cholesterol, and ischemic stroke in the general population. Ann Neurol. 2011;69(4):628-34. DOI:10.1002/ana.22384.
21. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke. 2009;40(4):1195-203. DOI:10.1161/STROKEAHA.108.529883.
22. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol. 2003;32(4):563-72. DOI:10.1093/ije/dyg106.
23. Tsivgoulis G, Safouris A, Kim DE, Alexandrov AV. Recent Advances in Primary and Secondary Prevention of Atherosclerotic Stroke. J Stroke. 2018;20(2):145-166. DOI:10.5853/jos.2018.00773.
24. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2003;34(3):623-31. DOI:10.1161/01.STR.0000057812.51734.FF.
25. Menet R, Bernard M, ElAli A. Hyperlipidemia in Stroke Pathobiology and Therapy: Insights and Perspectives. Front Physiol. 2018;9:488. DOI:10.3389/fphys.2018.00488.
26. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009;8(5):453-63. DOI:10.1016/S1474-4422(09)70058-4.
27. Yaghi S, Elkind MS. Lipids and Cerebrovascular Disease: Research and Practice. Stroke. 2015;46(11):3322-8. DOI:10.1161/STROKEAHA.115.011164.

Author's Contribution

MARA conceived the study idea, designed the research methodology, and contributed to data collection. FR assisted with data collection, performed statistical analyses, and contributed to manuscript writing. YA contributed to data collection and manuscript writing. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.