ORIGINAL ARTICLE

Atherosclerosis Surrogate Marker in Diabetic Patients

Seid Kazem Razavi-Ratki[1], Mona Kharaji [2], Nasim Namiranian[3], Mohammad Sobhan Ardekani[2],

Mahmood Emami[4], Amirpasha Amlelshahbaz[2], Karim Sharifi[5], Reza Nafisi Moghadam[6*]

1. Assistant Professor of Nuclear Medicine, Department of Radiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2. Department of Radiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Assistant Professor of Community Medicinet. Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
4. Department of Cardiology, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
5. Department of Radiology, Kurdistan University of Medical Sciences, Kurdistan, Iran
6. Associated professor, Department of Radiology, Shahid Sadooghi University of Medical Sciences, Yazd, Iran

*Correspondence:

Reza Nafisi Moghadam, Associated professor, Department of radiology, Shahid Sadooghi University of Medical Sciences, Yazd, Iran.
Tel: (98) 353 822 4000

Email: Nafisi.moghadam@gmail.com

Abstract

Objective: Duplex ultrasonography is a non-invasive, non-expensive screening test for carotid disease. Intima media thickness (IMT) is appropriate for atherosclerosis process diagnosis. Leukoaraisis (LA) increase the risk of cerebrovascular accident (CVA). LA patients need preventive medication for CVA. IMT is a non-invasive diagnostic and prognostic test in LA. The aim of this study was evaluate the carotid IMT and LA in diabetic patients as atherosclerosis surrogate marker.

Materials and Methods: The case-control study was done on 100 diabetic patients and 100 controls. They were selected by simple sampling method in Shaheed Sadoughi MRI unit. Two groups member were matched by age and sex. The patient's information (age, sex, weight, height, past medical history, smoking history, ischemic heart disease (IHD), CVA and past medication) according the study checklist was collected. All statistical analysis was done by SPSS21.

Results Totally 200 patients were studied, 102 in normal group and 98 in diabetic group. The mean age of patients was 64.39 (±9.12) and 47% participants were male. There were no statistical differences between hypertension and hyperlipidemia frequency in two groups (P-value>0.05). The mean of left CIMT was 0.856 (±0.202) in normal and 0.962 (±171) in diabetics groups (P-value: 0.026). The mean of right CIMT was 0.853 (±0.215) in normal and 0.973 (±188) in diabetics groups (P-value: 0.024). The LA was significantly more prevalent in diabetic patients (P-value:0.001).

Conclusion: LA increases the risk of CVA and dementia. The LA pathology is unknown. The epidemiological studies revealed the age, diabetes, smoking and atherosclerosis are related with LA. Our findings showed that CIMT as an atherosclerosis marker was higher in LA patients than control group.

Keywords: Leukoaraisis, Intima media thickness, Duplex ultrasonography, Diabetes.

Introduction

An increased carotid intima-media thickness was associated with cardiovascular risk factors, cardiovascular disease (CAD), and atherosclerosis in the arterial system (1-7). Leukoaraiosis (LA) is known as white matter changes (8). LA is associated with cognitive impairment (8-9), gait abnormalities, falls, and late-onset depression. LA is identified as hyperintensities in T2 sequences and fluid-attenuated inversion recovery (FLAIR) in magnetic resonance imaging (MRI) or

hypodensity with ill-defined margins in computed tomography (CT) in the areas of cerebral white matter (10-13).

LA is known as independent risk factor of stroke (14-15), poor stroke outcome (16). LA increases the risk of cerebro-vascular accident (CVA) (17-18). LA patients need preventive medication for CVA (19). Diabetes as CVA and CAD risk factor may be associated with LA. Although, increasing evidence indicates a relationship between carotid atherosclerosis and LA, but LA may be partially reversible in patients with carotid artery stenosis (20-23).

Intima media thickness (IMT) is appropriate for atherosclerosis process diagnosis especially in diabetic patients (24). Non-invasive assessment of IMT is widely used as an intermediate diagnostic tool in atherosclerosis process (25-26). There is a growing belief that carotid IMT can be used as an indicator of generalized atherosclerosis. Duplex ultrasonography is a non-invasive, non-expensive screening test for carotid disease. IMT may be useful as a non-invasive diagnostic and prognostic test for atherosclerosis diagnosis in diabetic patients (27-30). The aim of this study was evaluate the carotid IMT and LA in diabetic patients as atherosclerosis surrogate marker.

Materials and Methods

The case-control study was conducted on 100 diabetic patients and 100 controls. They were selected by simple sampling method in Shaheed Sadoughi MRI unit. Two groups member were matched by age and sex. The patient's information (age, sex, weight, height, past medical history, smoking history, ischemic heart disease(IHD), CVA and past medication) according the study checklist was collected.

To measure carotid intima-media thickness, ultrasonography of the common carotid artery, carotid bifurcation, and internal carotid artery of the left and right carotid arteries was performed with Sonoline G60 Model :Ay 15 CUZ ، Simens and Linear Array Transducer 7-10 MHZ. On a longitudinal, two-dimensional

ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space. The distance between the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness. LA was diagnosed by MRI. The imaging method was T2-weighted spin-echo [repetition time/echo time (TR/TE)=5800/96 ms], T1-weighted spin-echo (TR/TE=520/14 ms), and FLAIR (TR/TE=8500/96 ms; inversion time=2100 ms) images. LA was described as a focal lesion ≥2 mm in diameter, with hyper-intensity on T2-weighted and FLAIR images and without prominent hypo-intensity on T1-weighted images. The thickness of MRI slices was 4 mm, and 3 sections of the axial, sagittal, and coronal 2D views were used for LA diagnosis.

All statistical analysis was done by SPSS21.

Results

Totally 200 patients were enrolled (98 in diabetic and 102 in normal group). The mean age of participants was 63.39±9.12 years old. In diabetic group 51% were male and 49% were female and in control group there were 43% and 57%.

Table 1 describes general characteristics in two groups. Two groups IMT mean was compared. (table2). Additional analysis showed the risk ratio (RR) in right IMT>1, 7.12 with 95% confidence interval (2.48-17.99) and in left IMT>1, 8.82 (2.29-18.86).

Discussion

The findings in our study indicate that an increased common carotid intima-media thickness is associated with diabetes. Also the LA is more prevalent in diabetic patients. It is important to realize that there were no matching in atherosclerosis risk factors except age and sex.

Table 1. General characteristics in two groups

Variables	Diabetes Frequency (%)	Normal Frequency (%)	*P*-value
Hyperlipidemia	33(33.7%)	27(26.5%)	0.266
Hypertension	36(36.7%)	27(26.5%)	0.118
Carotid Plaque	38(38.8%)	20(19.6%)	0.003
Ischemic Heart Disease	37(37.8%)	22(21.6%)	0.012
La	52(53%)	28(27.5%)	0.001
Smoking	33(33.7%)	15(14.7%)	0.003

In Turk and et.al study findings was according with our findings (23). But in Saba study which was done in Italy there were significant differences between two groups (24). It should be noticed that there were no matching of atherosclerosis risk factors in two groups.

LA as an important public health problem increases the risk of stroke and dementia (25-27). The pathophysiology of LA in unknown, but LA is correlated with age, hypertension, arteriosclerosis, smoking, and diabetes in epidemiological studies (28-32). Also there is increasing evidence of relationship between large artery atherosclerosis and LA (32).

Our findings showed IMT is increased in diabetic group which was discovered by duplex sonography. The noninvasive assessment of common carotid intima-media thickness appears to provide a capable method to study the atherosclerosis risk factor in large populations (15-18).

As our study limitations, there were no group matching except age and sex for atherosclerosis. So in future studies, it should be considered.

Conclusions

The LA frequency was higher in diabetic patients. LA increases the risk of CVA and dementia. The epidemiological studies revealed the age, diabetes, smoking and atherosclerosis are related with LA. Our findings showed that CIMT as an atherosclerosis marker was higher in diabetic patients than control group.

References

1. Brisset M, Boutouyrie P, Pico F, Zhu Y, Zureik M, Schilling S, et al. Large-vessel correlates of cerebral small-vessel disease. Neurology. 2013;80(7):662-9.
2. Bots M, Hoes A, Koudstaal P, Hofman A, Grobbee D. Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction. Stroke A Journal of Cerebral Circulation. 1998;29(2):546.
3. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. American journal of epidemiology. 1997;146(6):483-94.
4. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke. 2006;37(1):87-92.
5. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incidence of stroke is related to carotid IMT even in the absence of plaque. Atherosclerosis. 2005;179(2):325-31.
6. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media

thickness. Journal of internal medicine. 20 257(5):430-7.

7. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke. 2004;35(12):2788-94.

8. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. circulation. 1986;74(6):1399-406.

9. De Groot E, Van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima–media thickness to assess progression and regression of atherosclerosis. Nature clinical practice Cardiovascular medicine. 2008;5(5):280-8.

10. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness a systematic review and meta-analysis. Circulation. 2007;115(4):459-67.

11. O'Sullivan M. Leukoaraiosis. Practical neurology. 2008;8(1):26-38.

12. De Leeuw F, de Groot JC, Achten E, Oudkerk M, Ramos L, Heijboer R, et al .Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. Journal of Neurology, Neurosurgery & Psychiatry. 2001;70(1):9-14.

13. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al. Incidental findings on brain MRI in the general population. New England Journal of Medicine. 2007;357(18):1821-8.

14. Group LS. 2001–2011: a decade of The Ladis (Leukoaraiosis and Disability) study: what have we learned about white matter changes and small-vessel disease? Cerebrovascular diseases. 2011;32(6):577-88.

15. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology. 2010;9(7):689-701.

16. Poels MM, Zaccai K, Verwoert GC, Vernooij MW, Hofman A, van der Lugt A, et al. Arterial stiffness and cerebral small vessel disease The Rotterdam Scan Study. Stroke. 2012;43(10):2637-42.

17. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney cause and logic of therapy. Hypertension. 2005;46(1):200-4.

18. Granér M, Varpula M, Kahri J, Salonen RM, Nyyssönen K, Nieminen MS, et al. Association of carotid intima-media thickness with angiographic severity and extent of coronary artery disease. The American journal of cardiology. 2006;97(5):624-9.

19. Cicorella N, Zanolla L, Franceschini L, Cacici G, De Cristan B, Arieti M, et al. Usefulness of ultrasonographic markers of carotid atherosclerosis (intima–media thickness, unstable carotid plaques and severe carotid stenosis) for predicting presence and extent of coronary artery disease. Journal of Cardiovascular Medicine. 2009;10(12):906-12.

20. Kozlov S, Balachonova T, Machmudova H, Tripoten M, Andreevskaya M, Rogoza A, et al. Carotid atherosclerosis, endothelial disfunction, and arterial stiffness in young and middle-aged men with coronary artery disease. International journal of vascular medicine. 2012;2012.

21. Streifler JY, Eliasziw M, Benavente OR, Alamowitch S, Fox AJ, Hachinski V, et al. Development and progression of leukoaraiosis in patients with brain ischemia and carotid artery disease. Stroke. 2003;34(8):1913-6.

22. Saba L, Sanfilippo R, Pascalis L, Montisci R, Mallarini G. Carotid artery abnormalities and leukoaraiosis in elderly patients: evaluation with MDCT. American Journal of Roentgenology. 2009;192(2):W63-W70.

23. Turk M, Pretnar-Oblak J, Zupan M, Zvan B, Zaletel M. Ultrasound diagnosis of carotid artery stiffness in patients with ischemic leukoaraiosis. Ultrasound in medicine & biology. 2015;41(1):64-71.

24. Saba L, Pascalis L, Sanfilippo R, Anzidei M, Bura R, Montisci R, et al. Carotid artery wall thickness and leukoaraiosis: preliminary results using multidetector row CT angiography. American Journal of Neuroradiology. 2011;32(5):955-61.

25. Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report a review. Stroke. 1995;26(7):1293-301.

26. Pantoni L, Simoni M, Pracucci G, Schmidt R, Barkhof F, Inzitari D, et al. Visual rating scales for age-related white matter changes (leukoaraiosis) can the heterogeneity be reduced? Stroke. 2002;33(12):2827-33.

27. Tarvonen-Schröder S, Röyttä M, Räihä I, Kurki T, Rajala T, Sourander L. Clinical features of leuko-araiosis. Journal of Neurology, Neurosurgery & Psychiatry. 1996;60(4):431-6.

28. Fu J, Lu CZ, Hong Z, Dong Q, Luo Y, Wong K. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(6):793-6.

29. Kissela B, Lindsell CJ, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, et al. Clinical prediction of functional outcome after ischemic stroke the surprising importance of periventricular white matter disease and race. Stroke. 2009;40(2):530-6.

30. Wiszniewska M, Devuyst G, Bogousslavsky J, Ghika J, van Melle G. What is the significance of leukoaraiosis in patients with acute ischemic stroke? Archives of neurology. 2000;57(7):967-73.

31. Longstreth W, Arnold AM, Beauchamp NJ, Manolio TA, Lefkowitz D, Jungreis C, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly the cardiovascular health study. Stroke. 2005;36(1):56-61.

32. Liao S-Q, Li J-C, Zhang M, Wang Y-J, Li B-H, Yin Y-W, et al. The association between leukoaraiosis and carotid atherosclerosis: a systematic review and meta-analysis. International Journal of Neuroscience. 2015;125(7):493-500.