RESEARCH ARTICLE

Differential effects of statins on matrix metalloproteinase-9 (MMP-9) in patients with acute ischaemic stroke: A potential for salutary

Marwa Their Naji, Hayder Mutter Al-Kuraishy, Ali Ismail Al-Gareeb

Abstract

Objectives: To illustrate the differential outcome of atorvastatin versus rosuvastatin on matrix metalloproteinases (MMP-9) in patients with acute ischaemic stroke (AIS).

Methods: The case-control study was done in the Department of Clinical Pharmacology and Therapeutic, Mustansiriyah University, Baghdad, Iraq, from March to June, 2020 and involved 66 AIS patients and 22 healthy controls. They sub-grouped into Group A: AIS patient on statins therapy (n=44), with 22 on atorvastatin and 22 on rosuvastatin. Group B: AIS patients not on statins therapy (n=22). Anthropometric, lipid, and pressure profiles were evaluated. As well, MMP-9 level was estimated in different treated groups. SPSS version 20.00 was used for data analysis.

Results: MMP-9 level was greater in patients with AIS (19.69±7.49 ng/dL) mainly those not on statin therapy (28.24±12.14 ng/dL) compared to the controls (10.54±1.92 ng/dL), (P=0.003). Regarding the differential effect of statins therapy on MMP-9 serum level in patients with AIS, it was (20.63±5.67 ng/dL) in patients on atorvastatin therapy and (19.69±5.41 ng/dL) in patients on rosuvastatin therapy, (P=0.57). MMP-9 serum level was highly correlated with stroke risk score (SRS) in patients with AIS not on statins therapy (P<0.001, r=0.89) as compared with SRS in patients with AIS on statins therapy (P=0.03, r=0.42).

Conclusion: MMP-9 is regarded as a surrogate biomarker of AIS in patients with underlying poor cardio-metabolic profile. Both atorvastatin and rosuvastatin are operative in attenuation of AIS measured by lowering of MMP-9 serum levels.

Keywords: Acute ischemic stroke, Statins, Matrix metalloproteinases. (JPMA 71: S-82 [Suppl. 8]; 2021)

Introduction

Stroke is a rapidly growing clinical disorder characterized by a rapid onset of focal and/or global neurological deficit, fixed more than 24 hours. The most reported type of stroke is acute ischaemic stroke (AIS), which represent 60-90.1%, followed by haemorrhagic stroke (HS), which includes subarachnoid haemorrhage (SAH) and intra-cerebral haemorrhage (ICH) and represent 10-30% of stroke patients.[1]

The risk factors for stroke including non-modifiable risk factors (gender, age, race, genetics and previous stroke history) and modifiable risk factors (diabetes, hypertension, smoking, alcohol intake, polycythemia and obesity).[2] In general, there are five unified sources of AIS that are large-artery atherosclerosis (thrombosis/ embolism), cardio-embolism, small-vessel occlusion (lacunae), undetermined etiology (cryptogenic), and other etiology like vasculitis. Cryptogenic stroke is a type of cerebral ischaemia without obvious origin and represents about 20% of all AISs.[3]

Department of Clinical Pharmacology, Medicine and Therapeutic, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq.

Correspondence: Hayder Mutter Al-Kuraishy. Email: hayderm36@yahoo.com

Different mechanisms are involved in the pathogenesis of AIS; increasing evidences show that ischaemic injury and inflammation are the central mechanisms in the pathogenesis and progression of AIS.[4] AIS triggers ischaemic cascades, which ultimately results in irreversible neuronal injury inside the ischaemic region.[5] AIS-induced neuro-inflammation is due to microglial activations at the acute stage of AIS that elicit an aggressive inflammatory reaction by release of pro-inflammatory cytokines including tumour necrosis factor (TNF-α), matrix metalloproteinase (MMP), chemokines and interleukins (IL-1β) and IL-6.[6]

MMPs are important group of proteolysis-associated enzymes; cleave fundamental structural elements that maintain blood brain barrier (BBB). Function of MMPs is regulated by specific MMP inhibitors, which are distributed in different tissues.[7] Among MMPs, MMP-9 is mainly involved in AIS and over-expressed by neutrophils adjacent to BBB in response to brain injury in AIS. Microglia, astrocyte, and endothelial cells increase MMP-9 expression following brain injury, which is involved in the initial pathological and late repairing events.[8]

Statins are a class of medications which inhibit HMG-Co-A

reductase, a rate limiting enzyme in cholesterol biosynthesis. The interruption of mevalonate pathway by statins is linked the pleiotropic effects of statins.[9] Farynsyl-pyrophosphate and geranylgeranyl-pyrophosphate are isoprenoid intermediates that are crucial for prenylation of specific GTPase proteins, which regulate cell differentiation and and cytoskeleton activities.[10] In addition, administration of statins during the acute stage of AIS may prevent stroke progression and relapse with reduction of post-stroke complications.[11]

Therefore, objective of the present study was to demonstrate the differential effect of statins on MMP-9 in AIS patients.

Patients and Methods

This case-control study was completed in the Department of Clinical Pharmacology and Therapeutic, Mustansiriyah University, Baghdad, Iraq, from March to June, 2020. This study was permitted by Scientific Committee and Editorial Board, College of Medicine, AL-Mustansiriyah University. A total of 88 participants (66 patients with AIS and 22 healthy controls) were involved in this study. The sample size was calculated according to the population size regarding 95% confidence interval and 5% marginal error. At first, 131 AIS patients were recruited, however, 65 of them were excluded due to haemorrhagic stroke (n=12), transient ischaemic attack (TIA) (n=13), acute renal failure (n=15), heart failure (n=9), malignancy (n=7), and liver cirrhosis (n=3). Therefore, only 66 patients were included, as shown in the consort-flow diagram of the present study (Figure-1). The included cohorts were hospitalized patients within 48 hours of focal neurological deficit, confirmed by computed tomography (CT) scan and magnetic resonance imaging (MRI). The selected 66 patients were initially subdivided into two groups following detailed medical history and physical examination.

Group A: AIS patients on statin therapy (n=44), either atorvastatin (n=22) or rosuvastatin (n=22).

Group B: AIS patients not on statin therapy (n=22).

Patients age $\geq$ 45 years, those with neurological symptoms of AIS within 48 hours, and with positive findings confirmed by MRI or CT.

Any patient having renal failure, heart failure, liver failure, thyroid disease, malignancy, head trauma, cerebral haemorrhage, TIA, pregnancy, lactation, and other chronic disorders were excluded.

Height and weight of patients were measured by anthropometric scales, body mass index (BMI) was calculated by the formula: BMI= Body Weight (kg) /Height (m^2). Blood pressure profile, including; systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by automated digital sphygmomanometer. Besides, mean arterial pressure (MAP) and pulse pressure (PP) were estimated by specific equations.[12]

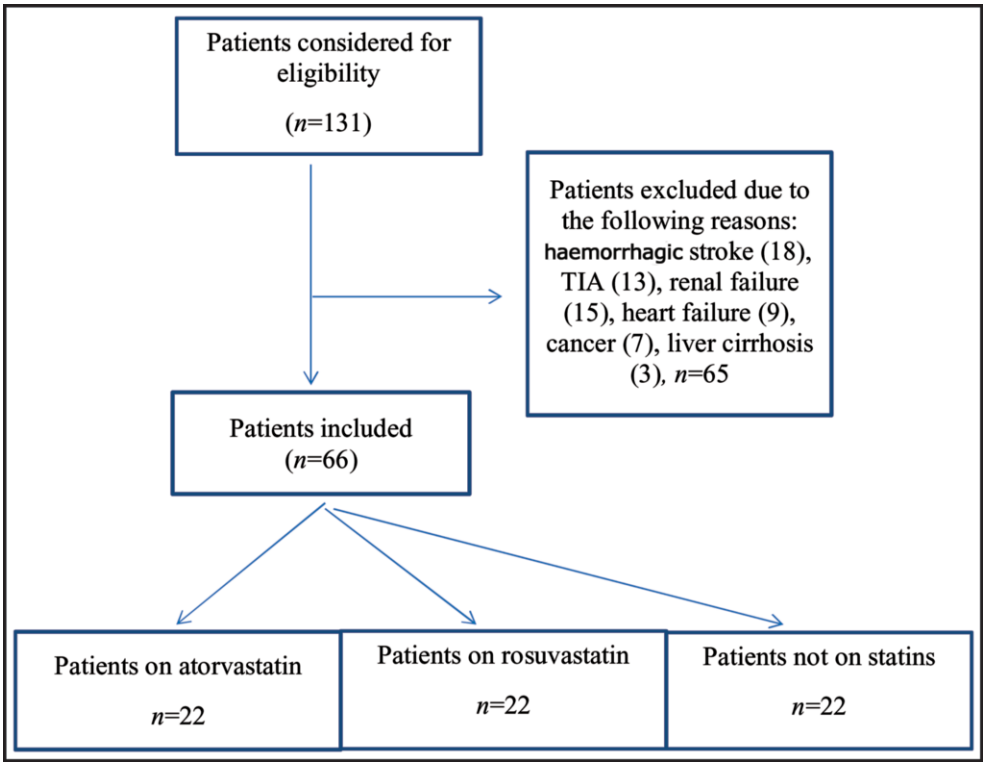


Figure-1: Consort-flow diagram of the present study.

Biochemical variables were tested by obtaining 5mL of blood sample after 12 hours overnight fasting. The blood samples were centrifuged at 3000/rpm and stored at (-20C°) to be utilized later. The study parameters included lipid profile (triglycerides (TGs), total cholesterol (TC), and high-density lipoprotein (HDL), by using instant cholesterol kit

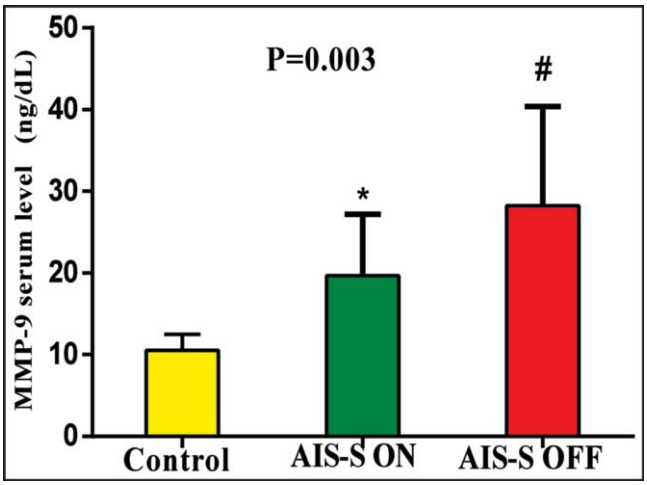
(Abbott, A.S.A) in ARCHITECT C 4000. While, low density lipoprotein (LDL), very low-density lipoprotein (VLDL) were calculated by the following equations; LDL=TC-HDL-(TG/5), VLDL= TGs/5. Atherogenic Index (AI) =log (TG/HDL), cardiovascular risk index (CVRI) = TG/HDL and cardiac risk ratio (CRR) =TC/HDL were estimated.[13] MMP-9 serum level was measured by utilizing an ELISA kit (MyoBio source, USA.) on the basis of sandwich method.

Stroke risk score (SRS) was evaluated according to the underlying cardio-metabolic risk factors according to Kate et al method.[14]

Data of the present study was analyzed by using SPSS version 20 and presented as means and standard deviations. Un-paired student t test was applied to detect the significance of differences between two groups. Besides, one way analysis of variance (ANOVA) and post-hoc test were applied to detect significance of differences among different treated groups. Level of significance was regarded when P value was less than 0.05.

Results

In the present study, 66(75%) of the enrollments were patients with AIS compared to 22(25%) healthy controls with a mean age of 67.81±12.84 years and nearly equal male-female ratio (51.13%-48.86%). Also 30(45.45%) of patients with AIS were cigarette smokers. The duration of AIS was short (days), and most of the patients presented with motor deficits and paralysis 32(48.49%), coma 8(12.12%), sudden visual loss 7(10.60%), and other neurological dysfunction like aphasia, dysphasia, dysphagia, delirium, and convulsion. Moreover, patients



***P <0.05 compared to statin off patients and control.**
#P<0.01 compared to the control.

Figure-2: MMP-9 serum level in patients with AIS regarding statins therapy as compared with the controls.

Table-1: Characteristics of the present study.

Variables	n, mean ±SD, %
N	88
AIS	66(75.00)
Control	22(25.00)
Age (years)	67.81±12.84
Gender (Male: Female ratio)	45(51.13):43(48.86)
Smoking	30(45.45)
Duration of AIS(days)	1.3±1.03
Clinical Presentation	
Coma	8(12.12)
Paralysis	32(48.49)
Visual loss	7(10.60)
Aphasia and dysphasia	6(9.09)
Convulsion	2(3.03)
Dysphagia	4(6.060
Delirium	7(10.60)
Associated diseases	
Dyslipidaemia	65(98.48)
Hypertension	66(100.00)
IHD	10(27.27)
Previous CVA	22(33.34)
Atrial fibrillation	4(6.06)
Dementia	2(3.03)
Parkinson disease	2(3.03)
Medications	
Statins	44(66.67)
Amlodipine	13(19.69)
ACEIs	8(12.12)
ARBs	14(21.21)
Antiplatelets	32(48.49)
β-blockers	32(48.49)

Data are expressed as N, mean±SD, %, M: F: male: female, IHD: ischaemic heart disease, CVAs: cerebro-vascular accidents, ACEIs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers.
#P<0.05 compared to the control.

with AIS were associated with different cardio-metabolic disorders including; hypertension 66(100%), dyslipidaemia 65(98.48%), ischaemic heart disease (IHD) 10(27.27%), previous CVAs 22(33.34%), AF 4(6.06%), and other neurological disorders such as dementia 2(3.03%) and Parkinson disease 2(3.03%). Concerning the associated and current pharmacotherapy, 44(66.67%) patients were on statins therapy compared with 22 (33.37%) patients not on statins therapy. According to the medical history of drug therapies, AIS patients also received but in an intermittent manner other medication such as anti-hypertensive and anti-platelet medications (Table-1).

BMI did not meaningfully vary between AIS patients and controls (P=0.34). Systolic blood pressure (SBP) was higher in AIS patients as compared to the controls (P=0.0001), however, it was inferior in AIS patients on

Table-2: Cardio-metabolic profile in patients with acute ischaemic stroke.

Variables	Control (n=22)	AIS (ST) ON (n=44)	AIS(ST) OFF (n=22)	ANOVA
BMI(kg/m^2)	31.87±3.12	31.00±4.47	32.74±5.90	0.34
SBP(mmHg)	130.78±9.07	143.63±12.92#	154.84±15.39*¶	0.0001
DBP(mmHg)	87.32±8.58	89.93±11.51	93.03±11.61	0.22
PP(mmHg)	43.46±6.91	53.70±4.09#	61.81±6.95*¶	0.0001
MAP(mmHg)	101.80±8.73	107.83±9.67#	113.63±11.59¶	0.003
TC(mg/dL)	214.45±30.12	210.66±21.96#	259.95±32.84*	0.0001
TG(mg/dL)	189.80±13.81	193.34±11.71	212.79±14.61*¶	0.0001
HDL-C(mg/dL)	53.79±8.47	48.92±9.06	34.91±5.93*¶	0.0008
non-HDL-C	160.66±21.78	161.74±20.99	225.04±23.81*¶	0.0001
LDL(mg/dL)	122.70±9.63	123.10±8.57	182.50±17.61*¶	0.0001
VLDL(mg/dL)	37.96±8.41	38.66±9.62	42.55±11.56	0.23
LDL/HDL ratio	2.28±1.08	2.51±1.09	5.22±2.05*¶	0.0001
AI	0.18±0.03	0.23±0.03#	0.42±0.06*¶	0.0001
CRR	3.98±1.72	4.30±1.12	7.44±2.81*¶	0.007
CVRI	3.52±1.06	3.95±1.86	6.09±2.84*¶	0.007

Data are presented as mean ±SD, ANOVA test and Tukey HSD Post-hoc Test, BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; TC: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; AI: atherogenic index, CRR: Cardiac Risk Ratio, CVRI: cardiovascular risk index; ST: statins.
¶*P <0.05 compared to statin therapy.

statins as compared with the patients with AIS not on statins therapy (P=0.03). While, the diastolic blood pressure (DBP) did not differ significantly in patients with AIS compared to the controls (P=0.22). Both PP and MAP were higher in AIS patients compared to the controls (P=0.0001) and (P=0.003) respectively. Alternatively, lipid profile (TC, TG, LDL, non-HDL) was higher in AIS patients compared to the controls (P=0.0001), though HDL-c was less in AIS patients compared to the controls (P=0.0001). Similarly, lipid profile ratio showed that LDL/HDL ratio, non-HDL-c, CRR, CVRI, and AI were higher in patients with AIS compared to the controls (P=0.0001), (Table-2).

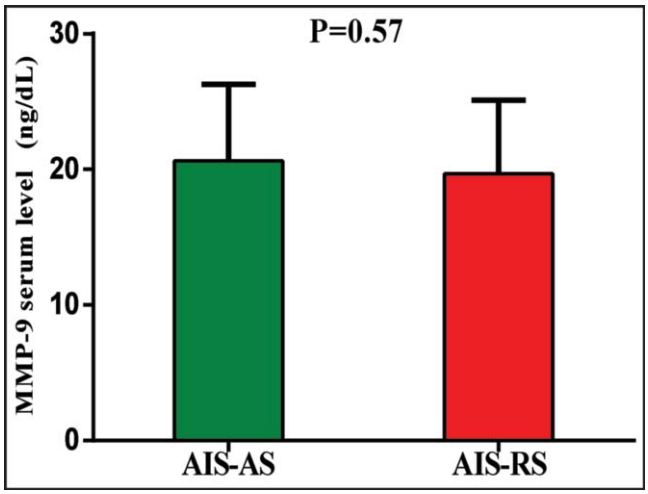


Figure-3: Differential effect of statins therapy on MMP-6 in AIS.

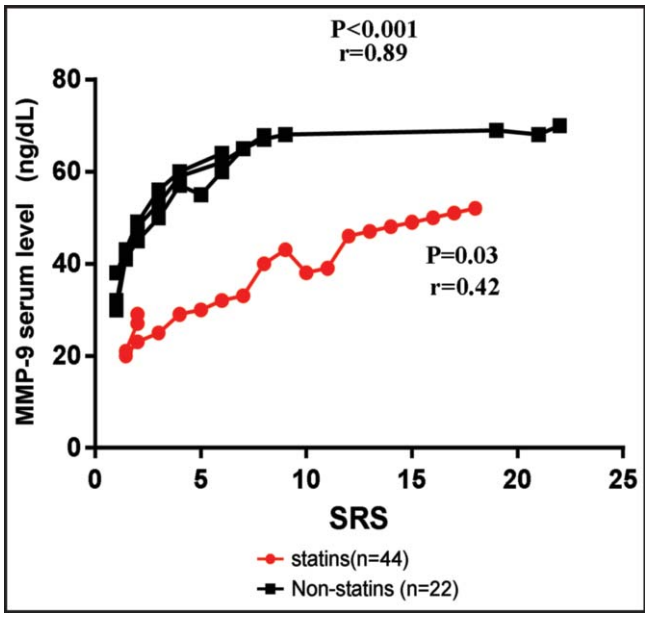


Figure-4: Correlation of SRS and MMP-9 serum level in patients with AIS regarding statins therapy.

MMP-9 level was higher in AIS patients (19.69±7.49 ng/dL) mainly in those not on statins therapy (28.24±12.14 ng/dL) compared to the controls (10.54±1.92 ng/dL), (P=0.003), (Figure-2). Regarding the differential effect of statins therapy on MMP-9 serum level in patients with AIS, it was (20.63±5.67 ng/dL) in patients on atorvastatin therapy and (19.69±5.41 ng/dL) in patients on rosuvastatin therapy, (P=0.57), (Figure-3). Moreover, MMP-9 serum level was closely associated with stroke risk score (SRS) in AIS patients not on statins therapy (P<0.001, r=0.89) as compared with SRS in patients with AIS on statins therapy (P=0.03, r=0.42), (Figure-4).

Discussion

Different factors affect the incidence of AIS, such as, gender, age, smoking, dyslipidaemia, hypertension, ischaemic heart disease and previous AIS.[15] In the present study, the mean age of AIS patients was 67.81±12.84 years). Yousufuddin and Young's[16] study showed that the ratio of AIS in patient older than 64 years was high. The most vigorous non-modifiable risk factor for stroke is aging, with the doubling of stroke incidence each ten years beyond 55 years. Aging triggers alterations in the functional and structural cerebral blood flow due to endothelial dysfunction, neuro-inflammation, and micro-vascular injury.[17]

In the present study, about half of the patients with AIS were cigarette smokers. Results from a recent meta-analysis showed that cigarette smokers have a higher risk of AIS as compared with non-smokers, since cigarette smoking increases the risk of AIS by 12% for each increase

of five cigarettes per day. Cigarette smoking triggers endothelial dysfunction, inflammation, lipid peroxidation, platelets activation, coagulation disorders, oxidative stress, and cerebral hypo-perfusion.[18]

BMI did not considerably differ between AIS patients and controls in the current study. It has been reported that increased BMI is independently associated with lower AIS risk; however, obesity is considered a risk factor for stroke in general population. The mechanism of obesity as a protective factor against stroke is unclear; though, it could be explained by the aggressive and earlier preventive treatments taken by obese patients with cardio-vascular risk factors.[19]

SBP was higher in AIS patients compared to controls (P=0.0001), however, it was lower in statins-ON AIS patients compared with statins-OFF AIS patients. DBP did not significantly differ between AIS patients and controls (P=0.22). Previous study estimated that statins act as BP-lowering agents due to increase of nitric oxide (NO) production, amelioration of endothelial function, anti-inflammatory effects, anti-oxidant effects, and anti-proliferative effects.[20] In the present study, PP and MAP were greater in AIS patients compared to controls, though high MAP, PP, and SBP are independent risk factors for AIS.[21]

Furthermore, serum lipid concentrations (TC, TG, LDL-c, non-HDL-c) were higher in AIS patients compared to controls, though, HDL-c serum levels were lower in AIS patients compared to controls. This result is consistent with the results of cohort studies in the field of AIS; that found an association between high serum cholesterol levels and risk of AIS. Moreover, an inverse relationship is found between HDL-c levels and risk of AIS. High LDL-c triggers endothelial dysfunction and atherosclerosis leading to cerebral hypo-perfusion, while high HDL-c provides a protection against the incidence of AIS.[22] Therefore, the present study illustrated that the underlying cardio-metabolic risk factors, mainly hypertension and dyslipidaemia, are strongly linked with the incidence of AIS.

On the other hand, in the present study, MMP-9 levels were significantly higher in AIS patients compared to the controls since; higher MMP-9 serum level is an evident factor in AIS patients. Following AIS, MMP-9 is over-expressed by microglia, endothelial cells, astrocytes, and neurons. MMP-9 degrades extracellular matrix components and stimulates leukocytes to enter the CNS.[23] MMP-9 is involved in both damage and repairing mechanisms, therefore MMP-9-targeted therapies might prevent an early damage and enhance late remodelling effect.[24] MMP-9 triggers the disruption of BBB resulting in extravasation of blood cells and plasma, with subsequent vasogenic oedema to provoke haemorrhagic transformation. High MMP-9 serum concentration during AIS is related to many complications, including large infarct volume, poor prognosis, and haemorrhagic transformation.[25] Therefore, MMP-9 can be used as a novel biomarker to predict post-ischaemic complications as haemorrhagic transformation.

Furthermore, measuring MMP-9 serum levels in patients with SAH, within 2 weeks from the start of haemorrhage, might predict the episode of delayed cerebral ischaemia. Some evidences suggest an association between MMP-9 gene polymorphism and risk of AIS since stroke patients with poor neurological consequences had higher MMP-9 serum concentrations compared to other patients.[26] Indeed, many studies described an increase in MMP-9 serum level in AIS patients within the first 24 hours after the start of ischaemia.[27] Keeping in mind the negative actions of MMP-9 in the course of AIS, along with some evidence showing its positive functions, it became obvious that using MMP-9 in the diagnosis of AIS is still unclear and needs further studies. Presently there are no studies indicating the effect of blocking of MMP-9 on stroke pathophysiology.

In the current study, MMP-9 serum levels were lower in statins-ON AIS patients compared to statin-OFF AIS patients as low MMP-9 might prevent micro-emboli development and stroke recurrence in post-stroke patients. Cecen et al., illustrated that previous statin treatment in AIS patients inhibit thrombolysis-induced elevation in MMP-9 level.[28] In addition, rosuvastatin lowers MMP-9 in a dose-dependent manner leading to noteworthy cardiovascular protection against inflammation-related changes, as well, intensive atorvastatin therapy reduces MMP-9 serum levels in AIS patients and other neurological disorders.[29]

This study had some limitations including a small sample size, outcomes of AIS patients were not evaluated, as well the sequential brain radiological changes were not evaluated in relation to the MMP-9 serum levels. Though, this study is considered as an introductory step for large forthcoming studies to assess the precise association between AIS and MMP-9 serum levels regarding statins pharmacotherapy.

Conclusion

MMP-9 is regarded as a surrogate biomarker of AIS in patients with underlying poor cardio-metabolic profile. Both atorvastatin and rosuvastatin are effective in attenuation of AIS measured by lowering of MMP-9 serum levels.

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