Statin therapy associated with decreased neuronal injury measured by serum S100β levels in patients with acute ischemic stroke

Hayder M. Al-Kuraishy, Ali I. Al-Gareeb, Marwa Thaier Naji

ABSTRACT

**Background:** Acute ischemic strokes (AIS) are a common cause of morbidity, mortality, and disability. The serum biomarker S100β correlates with poor neurological outcomes in the setting of AIS. This study describes the impact of statin treatment on S100β levels following AIS.

**Methods:** This was a prospective case–control study of AIS patients compared to healthy controls. Patients were stratified into three groups: (1) AIS patients on statin therapy, (2) AIS patients not on statin therapy, and (3) healthy controls. Demographics, clinical parameters, stroke risk scores (SRS), and S100β levels were recorded for all patients.

**Results:** Blood pressure, lipids, and SRS scores were higher in stroke versus control patients (all \( P < 0.05 \)), and lower in Group I versus II (all \( P < 0.05 \)). S100β levels were higher in stroke versus nonstroke patients (\( P = 0.001 \)), and lower in Group I versus II (\( P = 0.001 \)). Furthermore, patients on atorvastatin showed greater S100β reductions than those on rosuvastatin therapy (\( P = 0.01 \)).

**Conclusion:** In acute stroke patients, statin therapy correlated with reductions in the neuronal injury biomarker S100β, with greater reductions observed for atorvastatin than rosuvastatin therapy.

**Key Words:** Atorvastatin, rosuvastatin calcium, S100 calcium binding protein beta subunit, stroke

INTRODUCTION

Acute ischemic strokes (AIS) are a common cause of morbidity, mortality, and disability. The risk factors of AIS are divided into nonmodifiable risk factors (sex, age, inherited factors, ethnicity, and low birth weight at birth), and modifiable risk factors (diabetes mellitus, hypertension, smoking, obesity, alcohol abuse, oral contraceptive, and metabolic syndrome).

AIS is chiefly caused by thrombosis of cerebral vessels, causing cerebral ischemia, infarction, and induction of peri-infarct inflammatory. AIS leads to glucose and oxygen deprivation of neuronal cells, which, causes oxidative stress, excitotoxicity, and calcium overload, which eventually causing neuronal cell death and the development of an infarction core. The infarcted core releases different inflammatory molecules that cause damage of blood–brain barrier (BBB). Furthermore, this is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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microglia activation and macrophage infiltration increase inflammation and neuronal injury.\[^9\] Similarly, vascular smooth muscle and endothelial cells of cerebral vasculature activated through nuclear factor-kB (NF-kB) pathway leading to further obstruction and thrombosis. Therefore, the NF-kB pathway is an important pathway in the pathogenesis and development of neurological deficit.\[^6\]

In generally, microglia cells are inhabitant macrophages in the brain and acts as an active immune defense alongside with cerebral injury and infection, through induction and regulation of neuroinflammatory reactions. As well, microglia improve brain homeostasis and are responsible for the induction of neurogenesis and preservation of myelin sheath through secretion of neuroprotective factors such as insulin-like growth factor. Conversely, McDonough and Weinstein\[^7\] found that activated microglia leads to neuronal injury during acute ischemic reperfusion injury through the releasing of inflammatory and pro-inflammatory cytokines.

S100 calcium binding protein beta subunit (S100β) is a 21-kDa calcium-binding protein encoded on the long arm of chromosome 21, which is chiefly expressed by micoglia and astrocyte cells, also it is present in other neurological cells, including oligodendrocytes and neural progenitor cells. S100β is also expressed outside the brain mainly on melanocytes, chondrocytes, adipocytes, glial cells, dendritic cells, and supporting cells in the adrenal medulla, skeletal muscles, and arterial smooth muscles.\[^9\]

It released into the circulation following ischemic or hemorrhagic stroke, and traumatic brain injury. As a marker of BBB injury, S100β is released into systemic circulation following ischemic or hemorrhagic stroke, and traumatic brain injury, with levels reportedly correlating with poor neurologic outcome.\[^9,10]\] Serum level of S100β is increased within 6–12 h following AIS, and reaches the peak within 48–72 h. The biological half-life of S100β is 25.3 ± 5.1 min and subjected to the first-order kinetics. The elimination of S100β is 100% by the renal route. Time-dependent increase is 100% by the renal route. Time-dependent increase of S100β serum reflects specific fundamental complications, such as brain edema, infarction, and hemorrhage. Therefore, this biomarker is not dependable in patients with underling acute or chronic kidney diseases.\[^11,12]\]

S100β effects are concentration dependent. The normal functions of S100β are cell differentiation, inhibition of apoptosis, promotion of neuronal plasticity and neurogenesis, neuromodulation, regulation of memory and learning.\[^13\] At high concentration of S100β induces astrocytes and microglia to produce pro-inflammatory cytokines.\[^14\]

3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (i.e., statins) are used to treat hyperlipidemia. They have been observed to improve endothelial function prior to the improvement of total cholesterol (TC).\[^15\] Moreover, statins prevent and reduce the incidence of ischemic stroke in patients with coronary heart diseases from 2% to 30%.\[^16\] However, it is not obvious whether the neuroprotective effect of statins is attributed to a reduction of low-density lipoprotein (LDL) or to its pleiotropic effect. Recently, AlKuraishy et al.'s\[^17\] study, illustrated the neuroprotective effect of statins on the outcomes of AIS regardless of lipid-lowering effect. This study describes the impact of statins treatment on S100β levels following AIS.

**METHODS**

This was a prospective multi-center case–control study of AIS patients admitted to intensive care units at Al-Yarmook Teaching Hospital, Ministry of Higher Education and other medical centers in Iraq. The study was approved by the institutional review board and Ethical Committee according to IRB in 22 February 2020. The manuscript adheres to the “Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for reporting observational studies.”\[^18,19\] All AIS patients met the diagnostic criteria set forth in the American Academy of Neurology.

Participants were stratified into three groups: (1) AIS patients on statins therapy, (2) AIS patients not on statins therapy, and (3) healthy controls.

Statins therapy was defined as any treatment with a maintenance statins drug initiated ≥48 h prior to AIS. Participants whose statins therapy began <48 h prior to AIS were eligible for inclusion in the nonstatins group (Group II).

Exclusion criteria were hemorrhagic stroke, brain tumor, chronic stroke, transient ischemic attack, diabetes mellitus, hypothyroidism, chronic infection, sepsis, heart failure, rheumatic and connective tissue diseases, psychiatric and mental disorders, chronic liver dysfunctions, end-stage chronic kidney diseases. The exclusions depend on the detailed medical history, clinical examinations, routine investigations, and radiological investigations, including; brain computed tomography scanning (CT scans) and magnetic resonance imaging.

Anthropometric data were collected including height (Ht) in meter (m), body weight (BW) in a kilogram (kg) were calculated by graduate tape and digital electronic balance respectively, the body mass index (BMI) was calculated by specific equation, BMI = BW (kg)/Ht (m^2).\[^20\] Blood pressure profile, including systolic blood pressure (SBP), and diastolic blood pressure (DBP), was measured by automated digital sphygmomanometer, then, pulse...
pressure (PP), and mean arterial pressure (MAP) were calculated by specific equations according to the previous study, \( PP = SBP - DBP, MAP = SBP + 2(DBP)/3 \).[21]

**Biochemical variables**
A volume of 10 ml of venous blood samples was drawn after an overnight fasting from all patients and healthy controls, which centrifuged at 3000/rpm for 5 min, and stored in −20°C till the time of analysis.

Lipid profile, including TC, triglyceride (TG), and high-density lipoprotein (HDL), was measured by ELISA kit method (cholesterol, TG, HDL Assay Kit, Abcam, ab65390, Chicago, USA). LDL, very LDL (VLDL), Atherogenic Index (AI), \( AI = \log \frac{TG}{HDL} \) and cardiac risk ratio (CRR), \( CRR = \frac{TC}{HDL} - \frac{non-HDL-c}{c} = \frac{TC - HDL-c}{c} \), and cardiovascular risk index (CVRI) = TG/HDL were measured by specific equation according to a previous study.[22]

Serum levels of S100β were measured by ELISA kit method (SB100β ELISA Assay Kit, Abcam, ab234573, Chicago, IL, USA).

**Assessment of stroke risk score**
Stroke risk score (SRS) was performed using the age, lipid profile, blood pressure, and evidence of cardiometabolic disorders according to the American Stroke Association.[23]

**Statistical analysis**
Data analysis of 90 participants was done, using Statistical Package for the Social Sciences IBM® SPSS version 21 (IBM Corp., Armonk, Chicago, USA). Data were summarized using mean ± standard deviation for quantitative variables and frequency (%) for qualitative variables whether data were parametric or nonparametric. Un-paired Student’s t-test was used to determine the significance of differences between two groups, while one-way ANOVA test was used to find out the significance of differences among different groups.[24] Pearson correlation of S100β was used to find the significant correlations with the other parameters of the present study. The level of statistical significance was regarded when \( P < 0.05 \).

### RESULTS

Ninety patients were enrolled in the study. Three participants were excluded postenrollment [Figure 1].

Participants had a male predominance (79.3%). Only 12% of AIS patients had a family history of stroke and none of the enrolled healthy controls reported any positive family history for AIS, but 80% reported an active smoking history. Moreover, 39.65% of AIS patients were on statins therapy at baseline. About 81.03% of patients with AIS were active cigarette smoking compared with 28.68% controls \( (P = 0.001) \). Concerning the concomitant diseases in patients with AIS, most of them had different cardiometabolic risk factors, including hypertension (93.10%), asthma (6.89%), ischemic heart disease (IHD) (75.86%), and dyslipidemia (94.82%). Similarly, there was different pharmacotherapy used by recruiting patients, such as aspirin and clopidogrel as

| Table 1: Demographic characteristics of the study |
| The characteristics | Mean, SD, n (%) | \( P \) |
|---------------------|----------------|------|
| n                   | 87             |      |
| Patients            | 58 (66.67)     |      |
| Controls            | 29 (33.33)     | 0.003|
| Age (years)         | 59.67 ± 7.51   |      |
| Gender, male:female ratio | 46 (79.31): 12 (20.69) | 0.001|
| Race, W:B ratio     | 56 (96.55): 2 (3.44) | 0.0001|
| Family history      |                |      |
| Positive            | 7 (12.06)      | 0.0001|
| Negative            | 51 (87.93)     |      |
| Statins therapy     | 23 (39.65)     |      |
| Non-statins users   | 35 (60.34)     | 0.12 |
| Type of statins     |                |      |
| Atorvastatin        | 13 (56.52)     | 0.54 |
| Rosuvastatin        | 10 (43.47)     |      |
| Concomitant diseases|                |      |
| Hypertension        | 54 (93.10)     |      |
| Asthma              | 4 (6.89)       |      |
| IHD                 | 44 (75.86)     |      |
| Dyslipidemia        | 55 (94.82)     |      |
| Other pharmacotherapy|               |      |
| Aspirin             | 42 (72.41)     | 0.001|
| Clopidogrel         | 24 (41.37)     |      |
| Enoxaparin          | 3 (5.17)       |      |
| Theophylline        | 4 (6.89)       |      |
| ACEIs               | 34 (58.62)     |      |
| CCBs                | 22 (37.93)     |      |
| Metoprolol          | 31 (53.44)     |      |
| Smoking             |                |      |
| AIS patients        | 47 (81.03)     |      |
| Controls            | 6 (20.68)      |      |

Data are expressed as \( n, \) mean ± SD, W:B: White: black, IHD: Ischemic heart disease, ACEIs: Angiotensin converting enzyme inhibitors, CCBs: Calcium channel blockers, SD: Standard deviation
showed in Table 1.

**Cardiometabolic profile in patients with AIS**

BMI was across groups ($P>0.05$), SBP, DBP, and MAP were higher in strokes versus nonstroke participants ($P=0.001$), but similar between statin (Group I) versus nonstatin (Group II) groups ($P=NS$). PP did not differ across groups. PP did not differ across groups ($P>0.05$).

In addition, TC, TG, LDL-c, VLDL, and non-HDL-c were higher in stroke versus nonstroke participants ($P=0.001$), whereas patients in Group I had significantly lower values than those in Group II ($P=0.001$). HDL-c was lower in stroke versus nonstroke patients ($P=0.001$), and higher in Group I versus II ($P=0.001$). Moreover, AI, CRR, and CVRI were higher in stroke versus nonstroke participants ($P=0.001$), but AI and CVRI was lower in Group I versus II ($P=0.001$) whereas CRR did not differ significantly [Table 2].

The normal range of S100β serum level is 0.31–20 ng/ml, but in the present study this level was increased in patients with AIS as compared with the control (2.58 ± 1.03 ng/ml), $P=0.001$. S100β serum level in patients with AIS on statins therapy was lower (9.78 ± 2.75 ng/ml) as compared not on statins therapy (16.71 ± 4.38 ng/ml), $P=0.001$ [Figure 2a]. S100β serum level in patients with AIS on atorvastatin therapy was lower (11.99 ± 3.67 ng/ml) as compared with patients on rosuvastatin therapy (15.94 ± 3.12 ng/ml), $P=0.001$ [95% confidence interval 0.9736–6.9264], [Figure 2b].

SRS was highest among patients in Group II [$P=0.001$; Figure 3]. Moreover, SRS was more correlated with S100β serum levels in patients with AIS not on statins therapy ($P<0.001$, $r=0.89$) as compared with patients with AIS on statins therapy ($P=0.04$, $r=0.43$) [Figure 4]. Finally, SRS was lower in Group I patients on atorvastatin therapy (3.1 ± 0.89) as compared to rosuvastatin [4.11 ± 0.22; Figure 5].

**DISCUSSION**

The present study illustrated that most of the recruit patients were associated with cardio-metabolic risk factors such as hypertension, dyslipidemia, and IHD, which might increase the risk of AIS. Indeed, high CRR, AI, and CVRI in our patients with AIS compared to the control could explain the link between cardiometabolic risk factors and the risk of AIS. Daswaney et al. [23] found that the cardiometabolic risk factor increase the risk of AIS. About 56.89% of our patients were active smokers, which might augment the incidence and risk of AIS since, cigarette smoking is regarded as potential risk factor for...
AIS. As well, 12.06% of the recruited patients gave a positive family history of stroke compared to 87.93% with negative family history. Chung et al. revealed that early-onset stroke in relatives increase the risk of future stroke, implying that specific precautions are recommended in such populations. Low percentage of positive family history in our patients with AIS advocates us to exclude this factor in the present study.

In the present study, the percentage of AIS was low in patients that were on statin therapy compared with patients that were not on statins therapy, which might due to the neuroprotective effect of statin in the prevention and attenuation of AIS as showed by a recent study. Similarly, the present study observed that patients with AIS showed less cardiometabolic disturbances compared with those patients with AIS not were on statin therapy.

Statins improve lipid profile, endothelial function, and reduce the risk cardiovascular indices such as CRR, AI, and CVRI and consequently risk and incidence of AIS. Ever since its identification, S100β was used in the screening the outcomes and prognosis of traumatic brain injury and their requirements for brain CT scan. In the present study, S100β has been used to detect AIS-induced brain injury, and to observe the neuroprotective effect of statins through its spillover effect on S100β serum levels in stroke patients. In our study, patients with AIS, S100β serum levels were higher compared with healthy controls, as disclosed by Zhou et al. study which showed that S100β serum level is used as a prognostic biomarker in the evaluation and differentiation of AIS from a hemorrhagic stroke.

It has been reported that S100β is released from injured astrocyte during AIS within 15 seconds, and reach the peak within 24–48 h. As well, the concentration of S100β mRNA is also increased indicating that, the serum level of S100β is due to the release of store, and newly synthesis one.

In light of a considerable body of evidence demonstrating a link between S100β serum levels, and brain injury, it is essential to be aware that evidence of an association is not proof of causation. High serum levels of S100β have been attributed to an augmented passage of S100β from injured BBB, as it does not cross the intact BBB. Therefore, the initial high serum level of S100β in AIS as in the present study may not reflect the underlying neurological disorders since; S100β is important for neural regenerations. Therefore, high S100β serum level in our patients reflects either the passive release from damaged neurons or active release to counteract the neurological damage. Little is identified about BBB damage and cerebrospinal fluid (CSF) circulation during AIS. Nevertheless, changing in the choroid epithelial cells forming CSF has been observed, which lasting for 4 weeks following AIS. Thus, restoration of CSF-BBB function is correlated with better S100β passage and neurological functioning. Similarly, Branco et al. illustrated that serum level of S100β in the first 48 h in AIS predicts functional outcome at 12 weeks, regarding 150 ng/L as a cutoff value. A previous work has been shown that S100β serum level was correlated to S100β CSF level (which was 100 time higher than serum) and BBB injury. Disruption of BBB is evaluated through CSF: Serum albumin ratio, which is also correlated with S100β serum level. Moreover, Kleindienst et al. illustrated that BBB damage is not necessary for the passage of S100β to the serum. Damaged choroid plexus increase the reabsorption of S100β from CSF to the blood. However, reduction of serum S100β following brain damage may result from an increased need in damaged neurons. As well, Plog et al. found that S100β serum level is...
increased in AIS when BBB is intact, suggesting another pathway for the passage of S100β from CSF to the serum. This pathway is called glymphatic system which acts as brain lymphatic drainage. However, this system is also affected during AIS in the first 4 weeks following injury. Despite these controversies about the passage of S100β from CSF to the serum, a high increase in its levels is correlated with the underlying pathology of AIS.

Regarding the potential effect of statins therapy on S100β serum levels, to our knowledge, no previous studies discussed this context specifically. However, the present study illustrated that statins therapy, mainly atorvastatin reduced S100β serum in patients with AIS as compared with stroke patients not were on statins therapy. Yu et al.’s study demonstrated that prior treatment with atorvastatin reduce serum levels of pro-inflammatory mediators, mainly IL-6 and TNF-α in patients with AIS. This finding suggesting a neuroprotective effect of atorvastatin as revealed in our study. Moreover, Sanchez-Peña et al.[41] found that atorvastatin reduces serum levels of S100β in patients with ischemic stroke through attenuation of cerebral vasospasm and brain ischemia. Similarly, rosuvastatin also reduced S100β serum levels in our patients with AIS since; it protects neurons from acute ischemic changes through up-regulation of endothelial nitric oxide synthase in cerebral vasculatures.[42]

The question in this study was how statins reduced S100β serum levels in patients with AIS, and to answer this question, molecular level of inflammatory and pro-inflammatory mediators in AIS should be regarded. Since, the release and action of S100β are calcium-dependent, mainly cytosolic ca++2, a recent work illustrated that simvastatin inhibits cytosolic ca++2 in AIS, thereby may inhibits the release of S100β from ischemic neurons.[43] Indeed, statins inhibit acute activation of astrocyte cells in AIS, and other modalities of brain injury and prevent astrocyte cells for synthesis of new S100β.[44] These findings, might explain the low level of S100β in patients with AIS on statins therapy compared with nonstatins therapy.

Moreover, a higher concentration of S100β from damaged astrocyte cells leads to neuroinflammations through the activation of cytokine release from brain microglia. S100β activates brain microglia through the receptor of advance glycation end product (RAGE). RAGE is a surface molecule receptor play a role in the inflammatory process and induction of oxidative stress.[45] A recent study by Zhou et al. show that atorvastatin blocks RAGE pathway and blocking downstream signals of RAGE.[46] Therefore, statins block the action of S100β-mediated RAGE activation on the microglia in AIS. These findings might explain the direct or spillover effect of statins on S100β serum in patients with AIS. In fact, statins modulate S100β activity; render it at low rather than at high concentration in AIS, to be beneficial rather than harmful. This novel effect of statins is actually is part of the wide neuroprotective enigma of statins.[47]

The present study had different limitations; the sample size was relatively small, the severity of stoke was not taken into account, baseline comorbidities were not estimated, doses of statins were not considered precisely, and finally, the patient outcomes were not followed-up after the study period. Despite these limitations, this study is regarded as a base study discussing the relationship between statins and S100β serum levels in patients with AIS. Therefore, further studies are needed to confirm the association reported in this study.

CONCLUSION

Statins therapy in AIS reduced the biomarker of brain neuronal injury S100β, through potential spillover neuroprotective effect.

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Conflicts of interest

There are no conflicts of interest.

Research quality and ethics statement

This study was approved by the Institutional Review Board / Ethics Committee at Al-Mustansiriyia University College of Medicine, Baghdad, Iraq (Approval #56Y/22/1/2020; Approval date Feb 22, 2020). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE Guidelines, during the conduct of this research project.

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