Omentin-1: a biomarker in large artery ischaemic stroke patients

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Abstract

Background: Omentin-1 is a novel adipocytokine that is related to atherosclerosis-based ischaemic cardiovascular disease and stroke. Previous studies have linked its lower levels with poor stroke outcomes. We aimed to assess the level of serum omentin-1 as a prognostic marker in patients with large artery ischaemic stroke.

Methods: Fifty ischaemic stroke patients suffering large artery ischaemic stroke and another 50 subjects without a prior history of strokes were recruited. All participants were subjected to neurological examinations, echocardiography and laboratory investigations including a lipid profile and HBA1c. Carotid intima-media thickness (IMT) was measured for all participants. Stroke patients were evaluated by the National Institute of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). Infarction volume was measured by magnetic resonance image (MRI) and serum level of omentin-1 was gauged for all participants.

Results: Carotid IMT significantly increased in stroke patients compared to control subjects. While serum omentin-1 levels were higher in control non-diabetic subjects, they were lower in diabetic patients with ischaemic stroke. Serum omentin-1 levels were inversely correlated with NIHSS, carotid IMT, infarction volume and mRS scores in all stroke patients. Serum omentin-1 level less than 24.5 ng/ml showed 93.7% sensitivity and 44.4% specificity in prediction of poor stroke outcome while values less than 27.8 ng/ml in non-diabetic stroke patients had sensitivity and specificity with 87.5% and 55.6% respectively.

Conclusion: Lower levels of serum omentin-1 are associated with increased ischaemic stroke severity and poor functional outcome.

Keywords: Omentin-1, Ischaemic stroke, Adipokines, Biomarkers, Functional outcome

Background

According to recent estimates, the overall crude prevalence rate of stroke is 963/100,000 inhabitants [1]. Arterial stroke syndromes are characterised by a sudden loss of neurological function due to brain or retinal ischaemia representing 85% of stroke subtypes [2]. Large artery atherosclerosis is responsible for approximately 15–25% of all ischaemic strokes and it encompasses cervical artery atherosclerosis which affects the anterior (carotid arteries) or the posterior circulation (vertebral arteries) and intracranial atherosclerosis [3].

Stroke shares many risk factors with cardiovascular diseases, such as age, hypertension smoking and dyslipidaemias. The role of adipose tissue in ischaemic stroke remains largely unknown [4].

Omentin-1 is a recently identified adipocytokine of 313 amino acids expressed in visceral fat as well as mesothelial and vascular cells. The pathophysiological significance of plasma omentin-1 in atherosclerosis-based ischaemic stroke has not received much attention until recently [5].

Previous studies showed that serum omentin-1 levels decreased with obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM) and they were inversely correlated with parameters of obesity and metabolic risk factors [6, 7]. There was experimental evidence that circulating...
omentin-1 levels decreased in patients with established carotid atherosclerosis [8]. Therefore, plasma omentin-1 concentration may reflect vascular dysfunction to some extent, especially for diabetic patients. Recently, it has been reported that omentin-1 ameliorates ischaemic brain injury via promoting revascularization, inhibiting apoptosis and improving neural stem cells survival [9]. The current study aims to assess the level of serum omentin-1 as a prognostic biomarker in patients with large artery ischaemic stroke.

Methods
The current study was conducted at the Neurology and Medical Physiology Departments, Faculty of Medicine, for 6 months from the 1st of February till the end of July 2020. Fifty ischaemic stroke patients with large artery ischaemic stroke, clinically and radiologically confirmed according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [10], were recruited in the current study. They were distributed into two groups according to the presence of comorbid T2DM (group 1) or the absence of comorbid T2DM (group 2). Another 50 subjects who were age, sex and body mass index (BMI) matched to the ischaemic stroke patients without a history of previous cerebrovascular strokes were recruited as a control group. They were distributed into two groups according to the presence of comorbid T2DM (group 3) or the absence of comorbid T2DM (group 4).

Patients with a cardio-embolic stroke of other determined aetiology and with stroke of undetermined aetiology were excluded from the current study. Also, those with diseases that may affect omentin-1 plasma levels, such as systemic inflammation, neoplasm, heart failure, acute myocardial infarction or liver cirrhosis, were excluded. No one of the recruited stroke patients had received thrombolytic therapy as a prognostic biomarker in patients with large artery ischaemic stroke.

All stroke patients were subjected to magnetic resonance image (MRI) of the brain using Magnetom Sempra 1.5 Tesla, Siemens, Germany, during the 1st 24 h of admission to detect the infarction volume. The MRI examination included axial T1- and T2-weighted sequences, FLAIR sequence and diffusion-weighted images (DWI). The areas of the DWI abnormality were outlined manually on the MRI series. Initial cerebral infarction volume was measured on DWI and it was calculated as total hyperintense area in single slices multiplied by effective slice thickness [11].

Serum levels of omentin-1 were measured for all participants as the following: a blood sample was obtained after 10 h overnight fast and it was collected in polypropylene tubes. Serum was separated by centrifugation for 15 min and it was stored at −80 °C until being assayed for serum omentin-1 concentrations using human ELISA kits from Shanghai Enzyme-linked Biology Co., China. While serum omentin-1 was measured within 24 h of hospital admission in stroke patients [14].

An informed signed consent was obtained from all participants or their first-degree relative for the anonymous use of data and a consent for publication was also obtained. The study protocol was approved by the Research Ethical Committee, Faculty of Medicine, with number 32018/12/17.

Statistical analysis was conducted using SPSS Prism, version 20, 2011, created by IBM, Chicago, IL, USA. Statistical differences between the studied groups were examined using chi-square test for categorical variables and ANOVA/post-ANOVA tests for numerical ones. P-value <0.05 was considered statistically significant. Correlation analysis was performed using Pearson’s correlation test. Receiver operating characteristic (ROC) curve analysis was done for the determination of sensitivity and specificity of the cutoff values. The optimal cutoff was defined via the Youden index.

Results
Fifty large artery ischaemic stroke patients and another fifty subjects without previous cerebrovascular stroke were enrolled in the current study. They were distributed into four groups according to the presence or non-presence of comorbid T2DM. There were no statistically significant differences among the studied groups regarding their gender or smoking habits, while dyslipidaemias and hypertension were more common in stroke patients as illustrated in Table 1.
patients and control subjects, while HbA1c levels were significantly higher in diabetic patients and control subjects in comparison to non-diabetic participant as demonstrated in Table 2.

Regarding carotid IMT, there were statistically significant differences between stroke patients and control subjects. Further analysis by the post-ANOVA revealed a significant increase in IMT of diabetic stroke patients in comparison to non-diabetic stroke patients as shown in Table 3.

Regarding serum omentin-1 levels, they were higher in control non-diabetic subjects and lower in diabetic patients with ischaemic stroke. Also, there were statistically significant differences among the four groups concerning serum omentin-1 levels as illustrated in Table 4.

Regarding the evaluation of ischaemic stroke patients with NIHSS on admission and mRS after 3 months of stroke onset, no significant difference was observed between diabetic and non-diabetic patients, and this was also observed concerning initial cerebral infarction volume as shown in Table 5.

The results of our study revealed that serum omentin-1 levels in ischaemic stroke patients were significantly inversely correlated with NIHSS, carotid IMT, infarction volume and 3-month mRS scores in diabetic and non-diabetic patients as illustrated in Figs. 1 and 2 respectively.

Finally, serum omentin-1 level less than 24.5 ng/ml showed 93.7% sensitivity and 44.4% specificity in prediction of poor ischaemic stroke outcome after 3 months of follow-up and evaluation of disability by mRS in diabetic stroke patients, while the value less than 27.8 ng/ml in non-diabetic stroke patients had sensitivity and specificity with 87.5% and 55.6% respectively as illustrated in Fig. 3.

### Discussion
Omentin-1 is a novel adipokine identified in visceral adipose tissue, which is negatively correlated with different conditions such as obesity, inflammation, insulin resistance and type 2 diabetes. Fasting serum adiponectin levels have showed a similar variation trend to omentin-1, significantly lower in T2DM and impaired glucose

### Table 1 Gender and vascular risk factors between studied groups

|                      | Stroke patients | Control subjects | Chi-square |
|----------------------|-----------------|------------------|------------|
|                      | Diabetic        | Non-diabetic     |            |
|                      | Diabetic        | Non-diabetic     |            |
|                      |                |                  | $\chi^2$   | $p$-value |
| Sex                  |                 |                  |            |
| Males                | 13              | 15               |            |
|                      | 52%            | 60%              |            |
| Females              | 12              | 10               |            |
|                      | 48%            | 40%              |            |
| Dyslipidaemia        | 23              | 20               |            |
|                      | 92%            | 80%              |            |
| Smoking              | 15              | 16               |            |
|                      | 60%            | 64%              |            |
| Hypertension         | 20              | 20               |            |
|                      | 80%            | 80%              |            |

### Table 2 Differences in age, body mass index and glycosylated haemoglobin between studied groups

|                      | Stroke patients                         | Control subjects                         | Chi-square |
|----------------------|----------------------------------------|------------------------------------------|------------|
|                      | Diabetic                                | Non-diabetic                             |            |
|                      | Diabetic                                | Non-diabetic                             |            |
|                      |                                        |                                          | $\chi^2$   | $p$-value |
| Age in years         | Range 49–72                             | Range 48–75                              |            |
|                      | $\bar{X}\pm SD 60.8\pm6.56$            | $\bar{X}\pm SD 62.28\pm6.91$            |            |
|                      | 0.676                                   | 0.569                                    |            |
| BMI                  | Range 27.5–41.3                         | Range 29.7–41.21                        |            |
|                      | $\bar{X}\pm SD 30.92\pm2.58$           | $\bar{X}\pm SD 34.02\pm3.44$            |            |
|                      | 6.254                                   | 3.690                                    |            |
|                      | 0.001*                                  | 0.001*                                   |            |
| HbA1c on admission   | Range 6.9–9.8                           | Range 4.1–5.4                           |            |
|                      | $\bar{X}\pm SD 8.02\pm0.71$            | $\bar{X}\pm SD 4.74\pm0.38$            |            |
|                      | 308.13                                  | 308.13                                   |            |
|                      | 0.0001*                                 | 0.0001*                                  |            |

**BMI** body mass index, **HbA1c** glycosylated haemoglobin.
tolerance than in normal glucose tolerance [15]. Recently, serum omentin-1 levels were studied in cardiovascular, atherosclerosis and cerebrovascular stroke [6, 8, 16, 17].

We have conducted this study to investigate the promising role of serum omentin-1 as a novel biomarker in patients with large artery ischaemic stroke. Patients with cardio-embolic sources were excluded from the study because of the effect of these diseases on serum omentin-1 level [18]. It has been reported that serum omentin-1 levels are significantly lower in diabetic patients whether they are obese or not in comparison to normal subjects [19]. Based on these reports, our patients were classified into subgroups based on the presence or absence of comorbid T2DM. This was done to avoid the effect of T2DM on circulating serum omentin-1 levels.

The current study showed that serum omentin-1 levels were inversely correlated with carotid IMT in stroke patients. This is in agreement with the previous work of Shibata and colleagues in 2011 [20] as their results showed that circulating omentin-1 levels were negatively associated with carotid IMT, and they proposed that measurement of omentin-1 may be useful for the assessment of carotid IMT. This finding could be explained by the deleterious effects of low omentin-1 on vascular endothelial functions [21]. Another study conducted by Xu and colleagues in 2017 [7] reported that the higher levels of omentin-1 were inversely associated with carotid plaque instability, and it may represent a biomarker for predicting carotid plaque instability of acute ischaemic stroke patients. Omentin-1 suppresses tumour necrosis factor-stimulated cyclooxygenase-2 and it attenuates vascular inflammation. Omentin-1 also promotes endothelial nitric oxide synthase activation which has a protective role in the control of various vascular diseases including atherosclerosis [20].

Our results showed that serum omentin-1 levels were higher in control subjects in comparison to patients with ischaemic stroke. This is in agreement with a study done by Yang and Gao in 2020 [22] in which they found that serum omentin-1 levels were significantly lower in patients than in healthy controls. On the contrary to our results, Menzel et al. in 2016 [17] observed that the higher levels of omentin-1 were significantly associated with a higher risk of stroke. The different results could be explained by the methodological difference as they had recruited patients with previous cerebrovascular disorders including hemorrhagic stroke, cardiovascular diseases and metabolic syndrome.

Serum omentin-1 levels were correlated with stroke onset severity which was evaluated by NIHSS and infarction volume. The same finding was reported by Yue and colleagues in 2018 [23] as their study concluded that

| Table 3 Differences of carotid intima media thickness between studied groups |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                 | Stroke patients  | Control subjects |
|                                 | Diabetic        | Non-diabetic     | Diabetic         | Non-diabetic     |
| Carotid IMT                     | Range           | 1.1–1.6          | 0.87–1.5         | 0.79–1.4         | 0.69–1.89        |
|                                | M±SD            | 1.32±0.16        | 1.17±0.19        | 1.03±0.15        | 0.96±0.23        |
| f-value                        |                 | 17.41            |                  |                  |                  |
| p-value                        |                 | 0.0001*          |                  |                  |                  |

IMT intima media thickness

| Table 4 Differences of serum omentin-1 level between studied groups |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                 | Stroke patients  | Control subjects |
|                                 | Diabetic        | Non-diabetic     | Diabetic         | Non-diabetic     |
| Serum omentin-1 level           | Range           | 16.7–26.4        | 19.30–30.47      | 21.5–26.74       | 21.5–32.78       | 30.25–37.98      | 30.25–37.98      |
|                                 | M±SD            | 21.69±2.78       | 26.36±2.91       | 28.57±3.29       | 28.57±3.29       | 35.08±1.94       | 35.08±1.94       |
| f-value                        |                 | 97.7             | 2.91             | 3.29             | 3.29             | 1.94             | 1.94             |
| p-value                        |                 | 0.0001*          |                  |                  |                  |                  |                  |

ng/ml nanograms per millilitre

| Table 5 Differences of National Institute of Health Stroke Scale, initial cerebral infarction volume and modified Rankin Scale score between stroke patients |
|---------------------------------------------------------------------------------|------------------|
| Stroke patients                                                                 |                   |
| Diabetic                                                                        | Non-diabetic     |
| NIHSS                                                                           | Range           | 7–18             | 9–18             |
|                                | M±SD            | 31.64±2.15       | 13.24±2.42       |
| f-value                          |                 | 0.618            |                  |
| p-value                          |                 | 0.540            |                  |
| Initial cerebral infarction volume    | Range           | 15–47            | 24–48            |
|                                | M±SD            | 36.52±6.59       | 35.60±7.46       |
| t-value                          |                 | 0.463            |                  |
| p-value                          |                 | 0.646            |                  |
| mRS                               | Range           | 2–4              | 2–4              |
|                                | M±SD            | 2.69±0.78        | 2.92±0.75        |
| t-value                          |                 | 0.182            |                  |
| p-value                          |                 | 0.855            |                  |

NIHSS National Institute of Health Stroke Scale, mRS Modified Rankin Scale
Fig. 1 Correlations of serum omentin-1 level with National Institutes of Health Stroke Scale (NIHSS), infarction volume, carotid intima media thickness (IMT) and modified Rankin Scale (mRS) score in diabetic stroke patients.

Fig. 2 Correlations of serum omentin-1 level with National Institutes of Health Stroke Scale (NIHSS), infarction volume, carotid intima media thickness (IMT) and modified Rankin Scale (mRS) score in non-diabetic stroke patients.
levels of omentin-1 significantly reduced in stroke patients compared to control groups. Also, omentin-1 was related to lowered stroke risk representing an independent indicator for stroke severity. Despite recruiting heterogeneous stroke patients with different etiologies, serum omentin-1 levels were inversely correlated with both NIHSS and infarction volume [23].

Our results revealed that serum omentin-1 levels were significantly inversely correlated with mRS scores in diabetic and non-diabetic patients, indicating that patients with a low omentin-1 level at stroke onset had a poorer functional outcome. This result had been previously confirmed in 2018 by Xu et al. [14] who followed their stroke patients for 3 months and found that higher omentin-1 levels at baseline were negatively associated with poor functional outcome among ischaemic stroke patients. An interesting study by Wu et al. in 2019 found that a reduced level of serum omentin-1 was associated with poor functional outcome or death of non-diabetic patients with ischaemic stroke [24].

A recently published study evaluated the relation between omentin-1 and 1-y mortality after stroke. It concluded that high baseline serum omentin-1 was associated with a decreased risk of 1-y mortality [25]. The poor outcome related to lower omentin-1 level was thought to be mediated via insulin resistance and it enhanced inflammatory response even in non-diabetic stroke patients [25].

Different assumptions explain the protective roles of omentin-1 in stroke patients including improved vaso-dilation by endothelium-derived nitric oxide, and anti-inflammatory action derived from its ability to reduce the induction of migration, angiogenesis and activation of the activated protein kinase (AMPK) signalling pathway [23]. A preclinical study suggested omentin-1 could exert beneficial effects on mesenchymal stem cells by promoting proliferation, inhibiting apoptosis and increasing the secretion of angiogenic cytokines [26].

Finally, serum omentin-1 level showed high sensitivity and moderate specificity in the prediction of ischaemic stroke outcome after 3 months of follow-up and evaluation of disability by mRS in diabetic and non-diabetic stroke patients. The same findings were supported by the work of Yang and Gao conducted in 2020 [22] who found that higher plasma omentin-1 levels were negatively associated with poor functional prognosis of patients 90 days after acute cerebral infarction. These results confirmed what Yu et al. reported in 2019 [27] regarding the reasonable accuracy of omentin-1 to predict large artery ischaemic stroke outcomes. The different cutoff values among the different studies may be explained by different laboratory methods and different kits used in measuring serum omentin-1 levels in each study as well as the wide variation of normal serum level of omentin-1 (5 to 800 ng/mL) according to the manufacturer of the ELISA kit [28].

**Conclusion**

Lower levels of serum omentin-1 are associated with increased large artery ischaemic stroke severity and poor functional outcome at 3 months of stroke onset. Also, serum omentin-1 level represents a promising biomarker of ischaemic stroke functional outcome

**Study limitations**

A limited number of recruited patients were used as all subtypes of ischaemic stroke were excluded except patients with large artery stroke. Also those who received intravenous thrombolytic therapy or mechanical thrombectomy were excluded.

**Abbreviations**

AMPK: Activated protein kinase; DWI: Diffusion-weighted images; HBA1c: Glycosylated haemoglobin; IMT: Intima-media thickness; MRI: Magnetic resonance image; mRS: Modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; T2DM: Type II diabetes mellitus; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; BMI: Body mass index; CBC: Complete blood count; ECG: Electrocardiogram
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Declarations

Authors’ contributions
All authors have contributed in designing the study, acquisition of data, and data interpretation and revising. EN carried out laboratory evaluation and editing of the manuscript. OR recruited the patient, carried out clinical and neurological evaluation and participated in interpretation of the study results and editing of the manuscript. MÆ recruited patient, carried out clinical and neurological evaluation and participated in interpretation of the study results. AA recruited patient, carried out clinical and neurological evaluation and participated in interpretation of the study results. All authors have read and approved the manuscript.

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Availability of data and materials
All raw data will be available on the editor request.

Ethics approval and consent to participate
The study protocol was approved by the ethical committee in Tanta University, Egypt, under the code number (32018/12/17). Participation was the commencement of the study.

Consent for publication
Not applicable

Competing interests
The authors have no conflict of interest to disclose.

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