Research Square

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Salusin-α and Salusin-β as potential biomarkers in large artery atherosclerotic stroke

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Abstract

Objectives

Stroke is a leading cause of death and disability worldwide. The most common type of stroke is ischemic stroke, and the majority of these cases are caused by large-vessel atherosclerosis. The search for early stroke diagnostic biomarkers is ongoing. In this study, we investigated whether salusin-α and salusin-β, which are associated with atherosclerosis, could serve as biomarkers for predicting large-vessel atherosclerosis during the acute phase of stroke.

Methods

Fifty-one patients who presented to the emergency department with stroke symptoms, were diagnosed with large-vessel atherosclerosis, and arrived within the first 24 h of symptom onset were included. Additionally, 30 age- and sex-matched healthy volunteers were included as controls. In the stroke group, salusin-α and salusin-β levels were measured using ELISA within 24 h of onset and again at a 3-month follow-up. These values were compared over time and with those of the control group.

Results

Salusin-α levels measured in the first 24 h were significantly lower in the stroke group than in the control group ($p < 0.05$). No significant difference in salusin-β levels was observed. Over the 3-month period, salusin-β levels significantly decreased, whereas salusin-α levels remained unchanged. At follow-up, salusin-α levels remained significantly lower than those in the control group.

Conclusions

As salusin-α levels were consistently low in patients with stroke and did not change over time, this peptide may serve as a biomarker indicating susceptibility to stroke due to large-vessel atherosclerosis.

1. Introduction

Stroke is one of the leading causes of death and functional disability worldwide.[1]

Stroke is defined as an acute focal or diffuse cerebral injury and the resulting neurological deficit caused by a vascular event in the central nervous system, lasting more than 24 h or resulting in death. The majority of strokes (87%) are ischemic in nature.[2]

Large-artery atherosclerosis (LAA) is the most common subtype of ischemic stroke, and its underlying mechanism is atherosclerosis. Atherosclerosis is a modifiable risk factor for stroke[3]. Moreover, processes such as inflammation and infection have been independently associated with an increased risk of stroke.[4, 5] Detecting and managing modifiable risk factors early is important for patient survival, quality of life, and treatment costs.

Salusin-α and salusin-β, composed of 28 and 20 amino acids, respectively, are peptides synthesized from their precursor polypeptides, preprosalusin, and are characterized by potent hemodynamic and mitogenic activities. [6] Salusins are endogenously synthesized by multiple cell types and tissues such as the kidneys, vascular structures, central nervous system, monocytes, and macrophages.[6, 7] Salusins affect the components of atherogenesis, such as vascular inflammation, macrophage foam cell formation, vascular smooth muscle proliferation, and lipid balance. Additionally, they exhibit hypotensive and bradycardic effects on the cardiac system through the cholinergic system.[6] While Salusin-β promotes vascular inflammation and shows atherogenic effects, salusin-α has been shown in many studies to exert opposite, anti-atherogenic effects. [8–10]

Currently, no published study has examined salusin-α and salusin-β levels and their prospective course in acute ischemic stroke due to large vessel atherosclerosis. Our study aimed to elucidate the levels of salusin, which are hypothesized to be inflammatory markers, in the context of carotid atherosclerosis, an inflammatory process. Specifically, we aimed to determine whether salusin-β, which has been identified as atherogenic, and salusin-α, which has been identified as anti-atherogenic, could serve as biomarkers for acute stroke.

2. Materials and Methods

The study was initiated after obtaining approval from the Ethics Committee of Antalya Research and Training Hospital. (03.03.2020- 7/24) Participants were enrolled in the study between June 2020 and January 2021.

Subject:

Fifty-one patients who presented to our hospital with acute stroke and were found to have ≥ 70% carotid stenosis or occlusion upon evaluation were included in the study, provided that they presented within the first 24 h of symptom onset. Patients who were admitted > 24 h after the onset of initial symptoms were excluded from the study.

Blood was collected from the patients for biochemical tests, complete blood count, salusin-α and salusin-β levels, and serum samples were separated. At the follow-up 3 months later, blood was taken for routine control and salusin-α and salusin-β levels again

Eight patients died from stroke at follow-up, and 13 patients could not attend their follow-up after 3 months due to personal reasons. Blood was drawn from 30 patients for routine biochemical analysis, complete blood count, and salusin-α and salusin-β levels both within the first 24 h and 3 months later.

The control group consisted of patients who presented to the neurology outpatient clinic with complaints such as headache, dizziness, syncope, or tinnitus but were found to have no neurological disease upon examination and investigation. These patients had no history of cerebrovascular disease, and no carotid artery stenosis was detected on Doppler ultrasound examination. Routine biochemical

analyses, complete blood count tests, and serum samples for salusin-α and salusin-β were collected from these volunteers, who were similar to the stroke group in terms of age and sex. Subjects with a history

Patients with malignancy, hepatic or renal dysfunction, or active infection were excluded from the study.

Biochemical analysis:

Blood samples collected for salusin measurement were drawn into yellow-top serum separator tubes (SST) containing gel and centrifuged at 4000 rpm for 10 min to separate the serum. The obtained serum samples were stored at − 20°C until analysis. After all samples were collected, serum salusin-α (BT Laboratory, China; catalog no: E1268Hu; intra-assay coefficient of variation < 8%, inter-assay coefficient of variation < 10%) and salusin-β (BT Laboratory, China; catalog no: E1271Hu; intra-assay coefficient of variation < 8%, inter-assay coefficient of variation < 10%) levels were measured using the Enzyme Linked Immunosorbent Assay (ELISA) method. Analyses were conducted according to the procedures of these ELISA kits, standard curves were drawn, and the concentrations of the samples were calculated. The results were determined as pg/mL.

Complete blood count and biochemical tests were conducted at the SBÜ Antalya Training and Research Hospital laboratory. Glucose, blood urea nitrogen (BUN), creatinine, total cholesterol, triglycerides, HDL-cholesterol, and C-reactive protein (CRP) were analyzed using a spectrophotometric method with Beckman Coulter commercial kits on the Beckman Coulter AU5800 autoanalyzer (Beckman Coulter Inc., CA, USA). LDL cholesterol levels were calculated using the Friedewald formula. TSH levels were measured using chemiluminescence on a Beckman Coulter DxI800 (Beckman Coulter Inc., CA, USA). Glycosylated hemoglobin A1c (HbA1c) was analyzed using the liquid chromatography method with commercial kits on a Tosoh HLC 723 G8 (Tosoh Bioscience, Japan) device. Complete blood count (CBC) parameters and erythrocyte sedimentation rate (ESR) were analyzed using a Beckman Coulter LH780 hematology autoanalyzer.

Statistical analysis:

Statistical analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test. Categorical variables were expressed as frequencies (n) and percentages (%), whereas continuous variables were presented as mean ± standard deviation (mean ± SD).

Comparisons of categorical variables between groups were conducted using Pearson's chi-square test or Fisher's exact test, as appropriate. For continuous variables, between-group comparisons were performed using the independent samples t-test. A paired samples Student's t-test was used to compare the patients' values between the acute phase and the 3-month follow-up. Statistical significance was set at $p < 0.05$.

3. Results

The mean age of the 60 participants was 66.57 years, the male sex ratio was 40%, and the smoking rate was 16.6%. Hypertension was detected in 34 (56.6%) patients, diabetes mellitus in 10 (16.6%), coronary artery disease in 15 (25%), valve disease in 1 (1.6%), and atrial fibrillation in 1 (1.6%). Eighteen (30%) patients had unilateral stenosis and 12 (20%) had bilateral stenosis. There was no carotid stenosis in the 30 healthy volunteers. The mean age, sex, and prevalence of smoking did not differ significantly between the two groups. There were no differences between the two groups in terms of hypertension, diabetes, coronary artery disease, valve disease, and atrial fibrillation. Unilateral carotid stenosis was detected in 18 patients and bilateral carotid stenosis in 12 patients in the patient group, and no stenosis was observed in the control group. **(**Table 1**)**

Salusin-α and salusin-β levels in the patients in the first 24 h after stroke were compared with those in the control group. Salusin-α levels were significantly lower in the patient group than in the control group (p = 0.044), but no significant difference was found between the two groups in terms of salusin -β levels. **(**Table 2**)**

When salusin-α and salusin-β levels measured in the first 24 h after stroke were compared with the values measured 3 months after stroke, no significant change was observed in salusin-α levels. It was observed that salusin-β levels decreased significantly at 3 months. (p = 0.031) **(**Table 3**)**

When the salusin-α and salusin-β levels of the 3rd-month patient group were compared with those of the control group, salusin-α levels were found to be significantly lower in the patient group (p = 0.04), while no significant difference was observed in salusin-β levels between the two groups **(**Table 4**)**

Table 4
Serum Salusin Levels: Patients (3-Month Follow-up) vs. Control Group

Salusin-α (mean ± SD)	**Patients (chronic) n = 30**	**Control n = 30**	**p**
	131.49 ± 67.52	**179.14 ± 126.84**	**0.04***
Salusin -β (mean ± SD)	282.74 ± 176.09	247.44 ± 97.14	0.06
* Statistical significance			

In the correlation analysis between salusin-α and salusin-β levels and blood lipids in the first 24 h after stroke, no correlation was found between LDL-C, HDL-C, triglyceride, and HbA1c and salusin levels. While a weak negative correlation was found between salusin-α and total cholesterol (p = 0.023, r = − 0.29), a weak positive correlation was found between salusin-β and total cholesterol (p = 0.015, r = 0.31) **(**Table 5**)**

Table 5. Correlation analysis between salusin-α and salusin-β levels and blood lipids and HbA1c

		LDL	HDL	Triglyceride	Total cholesterol	HbA1c
Salusin-α	**r**	0.16	-0.02	0.107	**-0.29**	-0.82
(acute)	**p**	0.21	0.87	0.414	**0.023**	0.54
Salusin -β	**r**	0.17	-0.02	0.13	**0.31**	-0.109
(acute)	**p**	0.18	0.86	0.32	**0.015**	0.42

Table 1
Comparison of Demographic and Clinical Characteristics Between Patient and Control Groups

Age(year)	**Patient**	**Control**	**p**
	n = 30	**n = 30**	
	66.57 ± 10.85	**66.59 ± 10.13**	**0.994**
Gender- male, n (%)	10 (33.3)	14 (46.6)	0.455
Cigarette	8 (26.7)	2 (7.4)	0.083
Co-morbidities			
Hypertension n (%)	19 (63.3)	15 (50)	0.550
Diabetes mellitus n (%)	7 (23.3)	3(10)	0.304
Coronary artery disease n (%)	8(26.7)	7(23.3)	0.949
Valve replacement n (%)	1(3.3)	0	0.474
Atrial fibrillation n (%)	1(3.3)	0	1.000
Carotid stenosis			
Non stenotic n (%)	0	30(100)	
Unilateral n (%)	18(60)	0	< 0.001*
Bilateral n (%)	12(40)	0	

Table 2
Serum Salusin Levels: Patient Group (First 24 Hours Post-Stroke) vs. Control

Salusin-α (pg/mL)	**Patient (acute)**	**Control**	**p**
	(*n* 30)	**(*n* 30)**	
	125.43 ± 65.27	**179.14 ± 126.84**	**0.044***
Salusin -β (pg/mL	310.03 ± 191.03	247.44 ± 97.14	0.115

* Statistical significance

Table 3
Serum Salusin Levels: Acute Phase vs. 3-Month Follow-up

Salusin-α (mean ± SD)	**Patients (acute) n = 30**	**Patients (3rd month) n = 30**	**p**
	125.43 ± 65.27	**131.49 ± 121.52**	**0.314**
Salusin -β (mean ± SD)	310.03 ± 191.03	282.74 ± 176.09	0.031*

* Statistical significance

4. Discussion

The relationships between atherosclerosis, which underlies many leading causes of mortality, and salusin-β and salusin-α have been established in the literature [11, 12]. In our study, we found that salusin-α and salusin-β levels changed during the acute and chronic phases of acute ischemic stroke due to large artery atherosclerosis.

Hypertension is a major risk factor for atherosclerosis [13, 14]. Hypertension also increases the risk of stroke by contributing to cardiovascular disease [15]. In a study by Watanabe et al. Involving hypertensive patients and normotensive volunteers, the serum level of salusin-α was found to be lower in the hypertensive group. The plaque score and maximal intima-media thickness were higher in the hypertensive group than in the normotensive group, and more severe atherosclerosis was observed. A negative correlation has been found between the degree of carotid atherosclerosis and salusin-α levels [16]. In our study, salusin-α levels were low in both the acute and chronic phases in patients with carotid stenosis. Despite the low salusin-α levels in patients with essential hypertension in the same study, no direct correlation was found between blood pressure and salusin-α levels. In light of the current study and our findings, we propose that reduced salusin-α levels may be a potential biomarker for predicting atherosclerosis.

In a study conducted by Du et al., serum salusin-α levels were lower in the coronary artery disease group than in the control group. They also observed a negative correlation between salusin-α levels and the severity of coronary artery disease[17]. They suggested that salusin-α might have a cardiovascular protective effect and could be a potential biomarker for predicting the development and progression of coronary artery disease. In another study investigating the effects of salusins on atherosclerosis, no effect was found for salusin-β, whereas salusin-α was shown to play a preventive role in the pathogenesis of atherosclerosis by lowering total cholesterol levels [18]. In our study, we also found a negative correlation between total cholesterol and salusin-α and a positive correlation with salusin-β.

In our study, we found that salusin-α levels were lower in the carotid stenosis group than in the control group, which is consistent with previous studies. These results can be explained by two hypotheses. First, salusin-α may have a protective effect against atherosclerosis, and patients with low salusin-α

levels may be more prone to atherosclerosis and its complications, including stroke, because they cannot benefit from this effect. The second hypothesis is that in patients with atherosclerosis, salusin-α levels may decrease due to risk factors that predispose them to atherosclerosis or as a result of secondary pathophysiological mechanisms related to atherosclerosis that have not yet been fully explained.

In the study conducted by Arkan et al. [19], when patient groups were divided based on the degree of stenosis (%) and the number of affected vessels (single or double), no statistically significant difference was found in salusin-α levels between the groups. In our study, to ensure homogeneity, we only included patients who had experienced a stroke due to internal carotid artery atherosclerosis in the major vessels of the cerebral circulation. Although atherosclerosis of 50% or more is defined as large vessel disease in the literature, the degree of stenosis was 70% or more in almost all patients who presented to our center and were diagnosed with large vessel atherosclerosis. In a study conducted on patients with acute coronary syndrome, serum salusin-α levels were found to be inversely related to the severity of atherosclerotic heart disease. Patients with triple-vessel disease have lower salusin-α levels than those with single-vessel disease[11]. In our study, salusin levels did not significantly differ between patients with unilateral and bilateral carotid artery involvement. However, the small number of patients in the groups based on the number of affected vessels may have contributed to the lack of statistical significance in our study.

Another mechanism that could connect the salusins and stroke is inflammation. Esfahani, Movahedian, and colleagues [20] found that salusin-α suppressed pro-inflammatory cytokines and increased anti-inflammatory cytokines in human umbilical vein endothelial cells, highlighting the anti-inflammatory effects of salusin-α. In another study [19], a weak positive correlation was observed between salusin-β and hsCRP levels and between salusin-α and heregulin-β1 levels, an immunomodulatory factor. Zhou, Pan, and colleagues revealed that salusin-β induces inflammation [21]. Studies have demonstrated that inflammation underlies both the risk factors for stroke and the resulting conditions [22–27]. The pathophysiological changes that occur during stroke also increase inflammation and brain damage [4]. In our study, the low salusin-α levels in patients with stroke might initially be attributed to the relationship between stroke-related inflammation and salusin. However, the evaluation conducted at the 3rd month showed that salusin levels were not different from those measured in the acute phase after the stroke. This suggests that salusin-α levels may serve as indicators of underlying risk factors and chronic inflammatory processes rather than being markers of the acute inflammatory response.

Salusin-β has been suggested to be atherogenic due to its pro-inflammatory effects on the vascular endothelium in many tissues, including the brain[28][10] [29]. In our study, although salusin-β levels were higher in the patient group during the acute phase, the difference was not statistically significant. However, during post-stroke follow-up, salusin-β levels showed a statistically significant decrease. If larger studies can demonstrate that salusin-β levels are significantly elevated in stroke patients during the acute phase, the use of salusin-β, which is known to be an inflammatory biopeptide, as an acute phase marker for stroke may be considered. To definitively state that salusins are biomarkers of the

acute phase of stroke, further studies with larger patient populations are needed. These studies should monitor changes in salusin levels over days, hours, and even minutes.

In the literature, relationships between salusins and other neurological diseases and findings, besides stroke, have been investigated. In a study by Çakır et al. [30] on patients with Relapsing-Remitting Multiple Sclerosis (RRMS), an inflammatory and demyelinating disease, they found that salusin-α and salusin-β levels were higher than those in healthy controls, and they associated this elevation with the inflammatory process in the pathogenesis of the disease.

The role of salusins in the central nervous system and their relationship with neurodegeneration have been highlighted in a study on patients with Parkinson's disease, suggesting for the first time that salusin-β is an endogenous neuropeptide with neuroprotective effects against neurodegenerative diseases [31]. In another study, salusin-β levels were found to be significantly lower in Alzheimer's disease, Parkinson's disease, and acute ischemic stroke groups compared to the control group.[32] In our study, salusin-β levels in patients with stroke were higher in the acute phase than in the chronic phase. The increase in neuroprotective salusin-β release in response to tissue damage during a stroke may explain the elevation observed in the acute phase. Indeed, another study emphasized that reduced salusin-β, a peptide with neuroprotective effects, may contribute to the pathogenesis of Parkinson’s disease through chronically increased oxidative stress.[33] The lower levels of salusin-β in the chronic phase could be attributed to a reduction in salusin-β synthesis in the central nervous system due to cell death caused by the stroke. We believe that more extensive studies are needed to clarify the role of salusins in the pathogenesis of various neurological diseases.

One of the primary limitations of our study was the limited number of participants. Additionally, due to variations in the time patients presented to the emergency department after a stroke, uniformity in the timing of blood samples could not be achieved, and the acute phase progression of salusins could not be clearly demonstrated as measurements could only be taken once within the first 24 hours post-stroke.

In conclusion, in our study, we observed that salusin-α levels, which were low in the patient group during both the acute and chronic phases, did not change during follow-up. This suggests that salusin-α may be a biomarker indicating a predisposition to stroke rather than an acute phase marker. In contrast, we observed a significant decrease in salusin-β levels during follow-up after the acute phase. Although there was no significant difference in salusin-β levels between the patient and healthy groups in the acute phase, we believe that this may be due to the limited number of participants in our study. If future studies with larger sample sizes demonstrate a significant difference, salusin-β could potentially be used as a biomarker for the acute phase. To confirm the potential of salusins as acute-phase biomarkers in patients with stroke, further studies are needed with larger participant groups, frequent and sequential measurements of salusin levels following the acute phase, and investigations that shed light on the mechanisms underlying the relationship between salusins and stroke.

5. Conclusions

In conclusion, in our study, we observed that salusin-α levels, which were found to be low in the patient group during both acute and chronic phases, did not show any change during follow-up. This suggests that salusin-α may be a biomarker indicating a predisposition to stroke rather than an acute-phase marker. On the other hand, we observed a significant decrease in salusin-β levels during follow-up after the acute phase. Although there was no significant difference in salusin-β levels between the patient and healthy groups in the acute phase, we believe this may be due to the limited number of participants in our study. If future studies with larger sample sizes demonstrate a significant difference, salusin-β could potentially be used as a biomarker reflecting the acute phase. To confirm the potential of salusins as acute-phase biomarkers in stroke patients, further studies are needed with larger participant groups, frequent and sequential measurements of salusin levels following the acute phase, and investigations that shed light on the mechanisms underlying the relationship between salusins and stroke.

Declarations

Author Contributions: “Conceptualization, N.E, E.S.G.; methodology, N.E, E.S.G software, N.E, E.S.G.; validation, N.E, E.S.G and H.Y.E; formal analysis, N.E, H.Y.E ; investigation, N.E resources, E.S.G, N.E data curation, N.E, E.S.G and H.Y.E ;writing—original draft preparation, N.E, E.S.G.; writing—review and editing, N.E, E.S.G.; visualization, N.E, E.S.G.; supervision, N.E, ; All authors have read and agreed to the published version of the manuscript.”

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Institutional Review Board Statement:

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of University of Health Sciences (03.03.2020- 7/24 2020-091)

Informed Consent Statement: Informed consent was obtained from all the participants involved in the study.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.”

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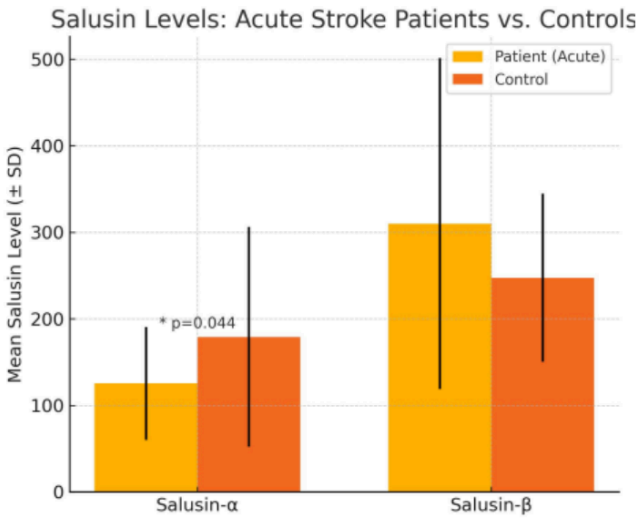
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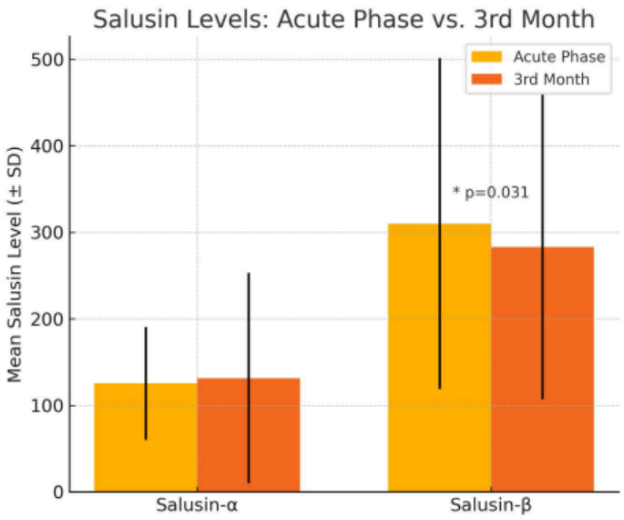
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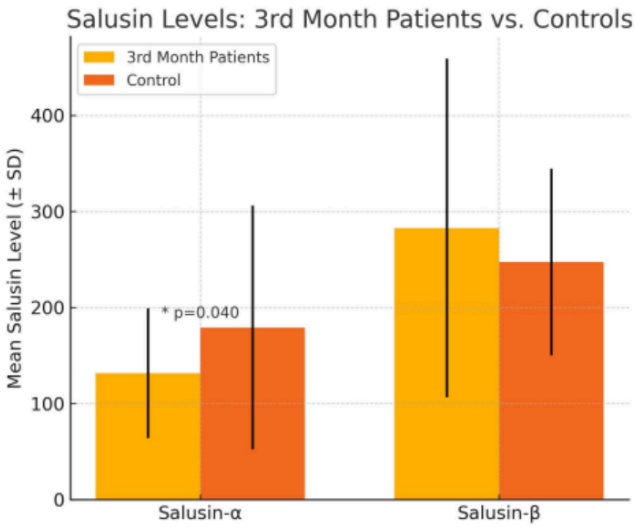
Figures



(a)



(b)



(c)

Figure 1

a) *Comparison of Salusin-α and Salusin-β levels between acute ischemic stroke patients (within the first 24 hours) and healthy controls. A significant reduction in Salusin-α was observed in patients (p = 0.044).*

b) *Salusin-α and Salusin-β levels in stroke patients at acute phase versus 3rd month follow-up. Salusin-β showed a significant decrease over time (p = 0.031), while Salusin-α remained stable*

c) *Comparison between stroke patients at the 3rd month and control group. Salusin-α levels were significantly lower in patients (p = 0.040), while the difference in Salusin-β was not significant.*