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RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

RELATIONSHIP BETWEEN INTRACRANIAL ARTERIAL CALCIFICATION AND SERUM ALKALINE PHOSPHATASE LEVELS

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ABSTRACT

INTRODUCTION: In this study, whether there is a relationship between serum ALP levels and intracranial arterial calcification was investigated.
METHODS: Here, 504 patients who applied to our hospital were included. These patients were divided into two main groups by whether they had intracranial arterial calcification (IAC) or not. Those with calcifications were divided into two subgroups (mild-moderate and severe calcifications) according to the their IAC burden. To calculate IAC burden on non-contrast brain CT, calcifications that were less than 50% of the intracranial vessels wall were assigned one point; and calcifications that were equal to or more than 50% were assigned two points for each artery (ICA, MCA, ACA, PCA, VA and BA) evaluated. Those with IAC burden less than three points were interpreted as mild-to-moderate calcification and those with more than or equal to 3 points were interpreted as severe calcification. Demographic characteristics, stroke risk factors, ALP levels and IAC burden of all groups were compared. The results were evaluated with chi-square, two independent samples t-test, Mann-Whitney U, Kruskal Wallis and Spearman's rho tests. Binary logistic regression analysis was also performed.
RESULTS: In this study, the average ALP level of the group with calcification (88,2 ± 28 U/L) was higher than the group of without calcification (60,4 ± 17,2 U/L) ($p < 0,05$). The average ALP level of severe calcification group (90,5 ± 28,4 U/L) was higher than the average ALP level of mild to moderate calcification group (78,4 ± 24 U/L) ($p < 0,001$). Stroke risk factors were significantly different between these groups. The patients with stroke risk factors had significantly higher ALP levels.
DISCUSSION AND CONCLUSION: Serum ALP levels were significantly higher in patients with IAC. IAC and ALP levels were higher in patients with high stroke risks. The presence of IAC and ALP elevations may be a predictor of increased stroke risk.
Keywords: Stroke, vascular calcification, ALP.

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İNTRAKRANİYAL ARTERİYEL KALSİFİKASYON İLE SERUM ALKALEN FOSFATAZ SEVİYELERİNİN İLİŞKİSİ

ÖZ

GİRİŞ ve AMAÇ: Bu çalışmada, intrakraniyal arteriyel kalsifikasyon (İAK) ile serum ALP seviyeleri arasında bir ilişki olup olmadığı incelendi.

YÖNTEM ve GEREÇLER: Burada, çeşitli sebeplerle iki yıl boyunca hastanemize başvurmuş olan 504 hastanın verileri incelendi. Hastalar İAK olanlar ve olmayanlar olarak iki ana gruba ayrıldı. Ayrıca kalsifikasyonu olanlar İAK yüküne göre "hafif-orta ve ciddi kalsifikasyonları olanlar" şeklinde iki alt gruba ayrıldı. İAK yükünü hesaplamak için kontrastsız beyin BT'de intrakraniyal damar duvarında %50'den az olan kalsifikasyonlara bir puan; %50 veya daha fazla olan kalsifikasyonlara iki puan verildi. Sonra bu puanlar toplanarak İAK yükü hesaplandı. İAK yükü üç puanın altında olanlar hafif-orta kalsifikasyon; üç ve üzerinde puanı olanlar ciddi kalsifikasyon olarak yorumlandı. Tüm grupların demografik özellikleri, inme risk faktörleri, ALP düzeyleri ve İAK yükü karşılaştırıldı. Bulgular ki-kare, bağımsız iki örneklem t testi, Mann-Whitney U, Kruskal Wallis ve Spearman's rho testleri ile değerlendirildi. Regresyon analiz yöntemi olarak binary logistik regresyon analizi uygulandı.

BULGULAR: Bu çalışmada, kalsifikasyonu olan grubun ALP ortalaması (88,2 ± 28 U/L); kalsifikasyonu olmayan grubun (60,4 ± 17,2 U/L) ALP ortalamasından daha yüksek bulundu (p <0,05). Ayrıca ciddi kalsifikasyonu olanların ALP ortalaması (90,5 ± 28,4 U/L); hafif-orta kalsifikasyonu olanların ALP ortalamasından (78,4 ± 24 U/L) daha fazla bulundu (p <0,001). Kalsifikasyonu olan ve olmayan gruplar arasında inme risk faktörleri açısından anlamlı bir fark elde edildi. İnme risk faktörleri olanlarda anlamlı olarak serum ALP değerleri yüksek bulundu.

TARTIŞMA ve SONUÇ: İAK'sı olanlarda serum ALP değerleri daha yüksek bulundu. İnme riski fazla olanlarda İAK görülmesi ve ALP düzeyi yüksekliği daha çok olmaktadır. İAK'nın varlığı ve ALP düzeyi yüksekliği inme riski artışının bir belirleyicisi olabilir.

Anahtar Sözcükler: İnme, vasküler kalsifikasyon, ALP.

INTRODUCTION

Alkaline phosphatase (ALP) is commonly known as an indicator of bone or hepatic diseases. Many studies have shown that vascular calcification and serum ALP levels are independently associated with stroke. The contribution of ALP explains this association to vascular calcification by catalyzing the hydrolysis of organic pyrophosphate. Organic pyrophosphate is an inhibitor of vascular calcification (1).

Studies evaluating the relationship between ALP and stroke have revealed that high ALP values are associated with poor prognosis and mortality after stroke (2,3). Larger-scale studies, in the meanwhile, have shown an independent relationship between ALP and stroke (4).

Chronic ischemia due to atherosclerosis is one of the major pathological mechanisms of cerebral small vessel disease (5). However, the course of small vessel disease varies greatly among patients with similar vascular risk factors (6,7). This suggests that possible unknown mechanisms contribute to atherosclerosis. Large-scale studies have shown an independent relationship between calcification in various vascular beds and cerebral small vessel disease (8,9). Vascular medial calcification, in particular, contributes to various cerebral events (LVH, white matter hyperintensity, cerebral microhemorrhages) by stimulating arterial stiffness (9,10). Vascular calcification, which can be easily detected on non-contrast brain CT, is also a predictor of coronary heart disease (11) and a potential marker of clinical stroke (12-14).

Thanks to its proven association with ALP, vascular calcification can play a role in the relationship between ALP and cerebral vascular disease (15). However, this association has not been demonstrated in intracranial arteries. In this study, the relationship between intracranial artery calcification load and serum ALP levels was investigated, and secondly, the relationship between these two parameters and stroke risk factors.

METHODS

The study was conducted under the Ethical Standards of the Declaration of Helsinki. It was approved by Kahramanmaraş Sütçü Imam University Scientific Research Ethics Committee (Session No: 2014/05, Decision No: 14, Date: 12.05.2014). The study is retrospective, hence signed consent was not obtained from the cases included in the study. This study was carried out

using the data of patients over the age of 18 who applied to our hospital with various complaints for two years, were followed up and treated on an outpatient and/or inpatient basis, and whose complete records were kept in the hospital's automation system.

Among these patients, those over the age of 18 and who had a brain CT scan for any reason were included in the study. According to their brain CT results, patients were divided into two main groups; with and without IAC. In addition, those with calcifications were divided into two subgroups as "mild-moderate and severe calcifications" according to the IAC load. Among the patients, those whose serum ALP levels were measured before or during the first week after the brain CT scan was identified.

Those who did not have a tomography or whose tomography image was not suitable for evaluation, those with a history of disease causing acute serum ALP elevation (hepatobiliary disease, sepsis, fracture, and bone-involving cancer history, and those with elevated serum total bilirubin, GGT, AST, and ALT), and those whose serum ALP level was not measured at the specified time were excluded from the study.

Evaluation of Intracranial Arterial Calcification: Hyperdense lesions over 90 Hounsfield units observed on the vessel wall of the intracranial arteries in the tomography brain imaging of the patients were evaluated as intracranial arterial calcification (IAC). Bilateral ICA, MCA, ACA, PCA, VAs, and BA arteries were evaluated one by one, and those with and without calcification were determined. Of the patients with circular calcification on the arterial wall in the ICA, BA, and VA arteries in the axial section on the brain tomography, those with calcification 50% or less of the arterial diameter were given one point, and those with 50% or more were given two points (Image 1). Of the patients with longitudinal calcification on the arterial wall in the MCA, ACA, and PCA arteries, those with calcification 50% or less of the arterial diameter were given one point, and those with 50% or more were given two points (Image 2). Those without calcifications were given zero points. For each patient, the IAC burden was obtained by summing all these scores. The minimum value of the IAC burden was set to zero and the maximum value to eleven (0-11). Patients with an IAC burden of zero points were considered to have no IAC, those with one or two points to have mild-moderate calcifications, and those with three or more points to have severe calcifications.

Demographic characteristics, serum ALP levels, stroke risk factors (HT, DM, HL, CAD, AF, smoking, previous stroke history), serum Ca, albumin, P, and creatinine levels of the patients were compared in two main groups, with and without calcification. Subgroups with mild-moderate and severe calcifications were also compared for differences in serum ALP levels. According to patients' demographic characteristics, stroke risk factors (HT, DM, HL, CAD, AF, smoking, previous stroke history), serum ALP values were compared, corrected Ca value, albumin, P, and creatinine levels. A relationship was sought between high CRP and calcification and ALP. In this study, 5 mg/l was accepted as the threshold value for CRP elevation. The ALP value of “32-92 U/L” obtained using the “Cobas c702, Roche” kit in the biochemistry laboratory of our hospital was accepted as the normal range for adults. ALP values above this range were considered high and included in the study.

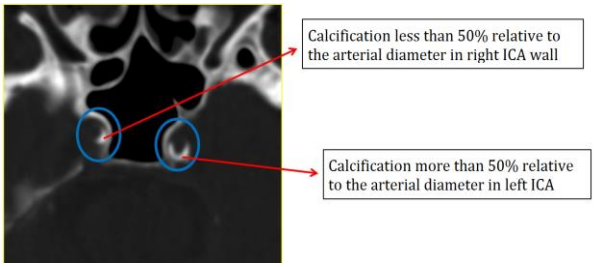

Image 1. In one patient included in our study, circular calcifications were observed in both internal carotid artery (ICA) walls on axial non-contrast brain tomography

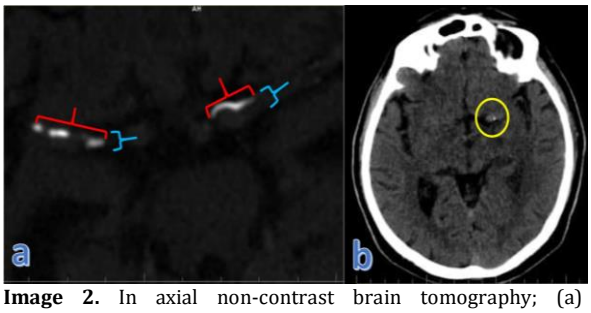

Image 2. In axial non-contrast brain tomography; (a) Longitudinal calcifications of more than 50% of the arterial diameter (blue brackets) are seen in both middle cerebral artery walls (red brackets). (b) Punctate calcifications of less than 50% of the arterial diameter are seen in the left middle cerebral artery wall (yellow circle).

Statistical analysis: Data were evaluated using the IBM SPSS (Statistical Package for Social Sciences) 20 software. For continuous variables, two independent samples t-test, Kruskal-Wallis test and Mann-Whitney U test as Post-hoc test; for categorical variables, Chi-Square test, and Mantel-Haenszel Common Odds Ratio Estimate analysis; for correlation, Spearman's rho test were used. Binary logistic regression was used for regression analysis. A p-value of <0.05 was considered significant in all analyzes.

Since age and creatinine are continuous variables, they were first converted to categorical variables. The patients were divided into two groups of similar size according to their age: under 70 years old (N= 198) and over 70 years old (N= 216). Regarding the creatinine level, values below 1.2 mg/dl constituted the normal, and above 1.2 mg/dl constituted the high creatinine group, based on our hospital's laboratory value (0.9-1.2 mg/dl). Then, binary logistic regression analysis was performed.

RESULTS

The study analyzed data of 504 patients. The patients were divided into two main groups as those with calcification (N=408) and those without (N=96). Those with calcifications were further divided into two subgroups: those with mild-moderate calcification (N=78) and those with severe calcification (N=330). Analyzes based on demographic characteristics of the participants detected no significant difference in gender distribution (F/M=47.1%/52.9%) (F/M=52.1%/47.9%) of patients with and without calcification (p=0.429). However, the mean age of these two groups was significantly different from each other (p <0.05). The mean age of the groups with and without calcification was 70.9±12.9/year and 38.9±14.2/year, respectively. The mean age of those with high serum ALP levels (N=178; >92 U/L) and normal serum ALP levels (N=526; 32-92 U/L) were 66.9±15.9, and 57.2±19.7 years, respectively. There was a significant (p=0.000) but weak correlation between age and serum ALP levels (Spearman rho=0.208). There was no significant relationship between gender and serum ALP levels (M=78.5±24.1 U/L; F=79.6±28.3 U/L; p=0.962).

The relationship between the patients' admission diagnosis and calcification is given in Table 1.

Table 1. Relationship between admission diagnosis and calcification.

Admission diagnosis	Calcification
Acute altered consciousness (syncope, delirium, epileptic seizure, mild confusion, coma)	50.2% (N= 205)
Headache	10% (N= 41)
Dizziness	8.1% (N= 33)
CVD	31.6% (N= 129)

CVD; cerebrovascular disease.

The mean ALP level of the group with calcification (88.2±28 U/L) was significantly higher than the group without calcification (60.4±17.2 U/L) (p<0.05). Besides, the mean serum ALP was significantly higher in patients with severe calcification (N=330; mean ALP 90.5±28.4 U/L) compared to those with mild-moderate calcification (N=78; mean ALP 78.4±24 U/L) (p<0.001).

Comparison of stroke risk factors in the groups with and without calcification revealed a significant difference between these two groups in terms of risk factors (CVD, DM, HT, CAD, AF, CKD, and HL) except smoking (p<0.001). In those with calcifications, CVD (62.3%), DM (34.3%), HT (72.5%), CAD (43.9%), AF (10%), CKD (21.3%), and HL (35.8%) risk factors were seen at a higher rate. Among those with calcification, 41 were smokers, while only six without calcifications were smokers. However, the relationship between smoking (N=47) and calcification was not significant (p>0.05).

Analysis of the groups with and without calcification in terms of serum phosphorus, calcium, albumin, and creatinine levels detected no significant difference between these two groups in terms of mean phosphorus and calcium levels (p>0.05). However, mean albumin levels (p=0.010) were higher in the group without calcification, and mean creatinine levels (p=0.000) were higher in the group with calcifications.

Analysis of the relationship between calcification and CRP showed that CRP level was higher in 72.8% (N= 46) of those with calcification. CRP level was higher in 52.6% (N= 0) of those without calcification. As a result, CRP was determined to be significantly higher in patients with calcification (p<0.05).

In the analysis of the relationship between serum ALP values and stroke risk factors, the mean serum ALP of those with CVD (N=274) (85±29 U/L) was slightly higher than the mean serum ALP of those without CVD (N=230)

(80.2±27.7 U/L) (p>0.05). In patients with DM, HT, CAD, CKD, and HL risk factors, serum ALP values were significantly higher (p<0.05), but there was no significant difference in terms of smoking and AF (p>0.05). In addition, only the mean serum creatinine was significantly higher in the group with high ALP (p=0.010), but their correlation was weak (Spearman's rho value of 0.150).

Analysis of the relationship between ALP and CRP revealed significantly higher mean serum ALP in the high CRP group (N=286) (84.3±27.9 U/L) than in the normal CRP group (N=128) (77.9±27.9 U/L (p=0.010).

Finally, a statistically significant relationship was observed between intracranial arterial calcification and serum ALP levels, independent of stroke risk factors (Age, DM, HT, CAH, AF, HL, Smoking, Stroke history) and CRP elevation (e.g., excluding age, Mantel-Haenszel OR=9.339; p=0.000). However, HL and AF were not found to contribute to intracranial arterial calcification. The effect of HL was insignificant when HT was excluded (Mantel-Haenszel OR=1.76; p=0.152).

The effect of AF disappeared when HT (OR=5.36; p=0.088), CAD (OR=4.64; p=0.132) and CRP levels (OR=6.44; p=0.67) were excluded (p<0.05). Similarly, the effect of HL on serum ALP levels was not observed when CAD was excluded (OR=1.54; p=0.60).

The binary logistic regression analysis determined that patients with calcification had 8.4 times higher ALP elevation, 3.1 times higher HT frequency, 6.2 times higher DM, three times higher stroke history, 20.5 times higher age than patients without calcifications (p<0.05).

The relationships between intracranial arterial calcification, serum ALP levels, and stroke risk factors are summarized in Table 2, and binary logistic regression analysis results are summarized in Table 3. The comparison of the mean serum P, Ca, albumin and creatinine in the calcification and ALP groups is shown in Table 4; the distribution of calcifications according to the arterial tree is shown in Figure 1; the mean serum ALP levels according to the calcification severity are shown in Figure 2.

Table 2. Relationship between intracranial arterial calcification, serum ALP levels, and stroke risk factors.

Groups		Without Calcification	With Calcification	p	Serum ALP mean (>92 U/L)>	p
Age (years)		38.9 ± 14.2	70.9 ± 12.9	.000	66.9 ± 15.9	.001
Gender	Female	50 (52.1%)	192 (47.1%)	.375	79.6±28.3	.962
	Male	46 (47.9%)	216 (52.9%)		78.5±24.1	
CVD	Yes	20 (20.8%)	254 (62.3%)	.000	85 ± 29	.079
DM	Yes	4 (4.2%)	140 (34.3%)	.000	87.9 ± 27.3	.004
HT	Yes	19 (19.8%)	296 (72.5%)	.000	86.3 ± 29.1	.001
HL	Yes	10 (10.4%)	146 (35.8%)	.000	89.7 ± 29.7	.000
AF	Yes	1 (1%)	41 (10%)	.004	89.4 ± 28	.088
Smoking	Yes	6 (6.2%)	41 (10%)	.249	81.6 ± 24.5	.951
CKD	Yes	11 (11.5%)	87 (21.3%)	.028	91.4 ± 35.7	.023
CRP	High	52.6%	72.8%	.001	84.3 ± 27.9	.010

ALP; alkaline phosphatase, CVD; cerebrovascular disease, DM; diabetes mellitus, HT; hypertension, HL; hyperlipidemia, AF; atrial fibrillation, CKD; chronic kidney disease, CRP; C reactive protein.

Table 3. Binary logistic regression analysis.

Variables	p	OR	95% Confidence Interval	
Gender*	.648	.845	.410	1.741
DM	.003	6.185	1.825	20.955
HT	.010	3.052	1.308	7.122
CAD	.874	1.096	0.353	3.406
AF	.777	.714	.069	7.370
Smoking	.600	1.518	.319	7.225
HL	.835	1.117	.396	3.152
CRP	.756	1.128	.528	2.408
CVD	.004	3.047	1.421	6.532
CKD	.321	.445	.090	2.199
ALP	.000	8.386	2.830	24.850
Creatinine	.450	1.745	.412	7.397
Age	.000	20.476	7.231	57.982

DM; diabetes mellitus, HT; hypertension, CAD; coronary artery disease, AF; atrial fibrillation, HL; hyperlipidemia, CRP; C reactive protein, CVD; cerebrovascular diseases, CKD; chronic kidney disease, ALP; alkaline phosphatase.

Table 4. Comparison of mean serum P, Ca, albumin and creatinine in calcification and ALP groups.

	Without Calcification	With Calcification	p	High ALP	Normal ALP	p
P	3.2 ± 0.8 mg/dl	3.4 ± 0.9 mg/dl	.119	3.3 ± 0.8 mg/dl	3.3 ± 0.9 mg/dl	.550
Ca (adjusted)	9 ± 0.5 mg/dl	9.1 ± 0.8 mg/dl	.097	9.1 ± 0.9 mg/dl	9 ± 0.6 mg/dl	.619
Albumin	3.7 ± 0.7 mg/dl	3.5 ± 0.6 mg/dl	.010	3.6 ± 0.6 mg/dl	3.6 ± 0.6 mg/dl	.976
Creatinine	1 ± 1 mg/dl	1.6 ± 2.3 mg/dl	.000	1.7 ± 1.9 mg/dl	1.4 ± 2.3 mg/dl	.010

P; phosphorus, Ca; calcium, ALP; alkaline phosphatase.

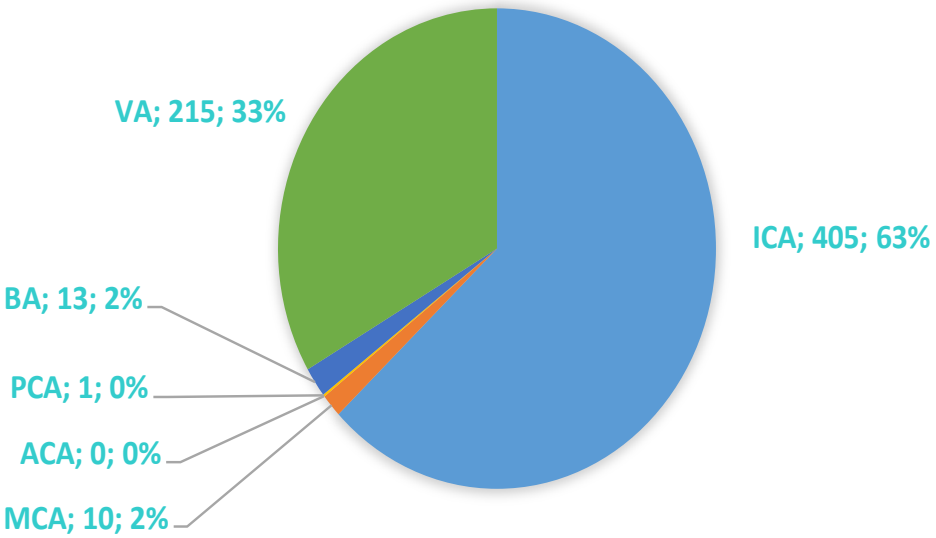

Figure 1. Distribution of calcification within the arterial trees.

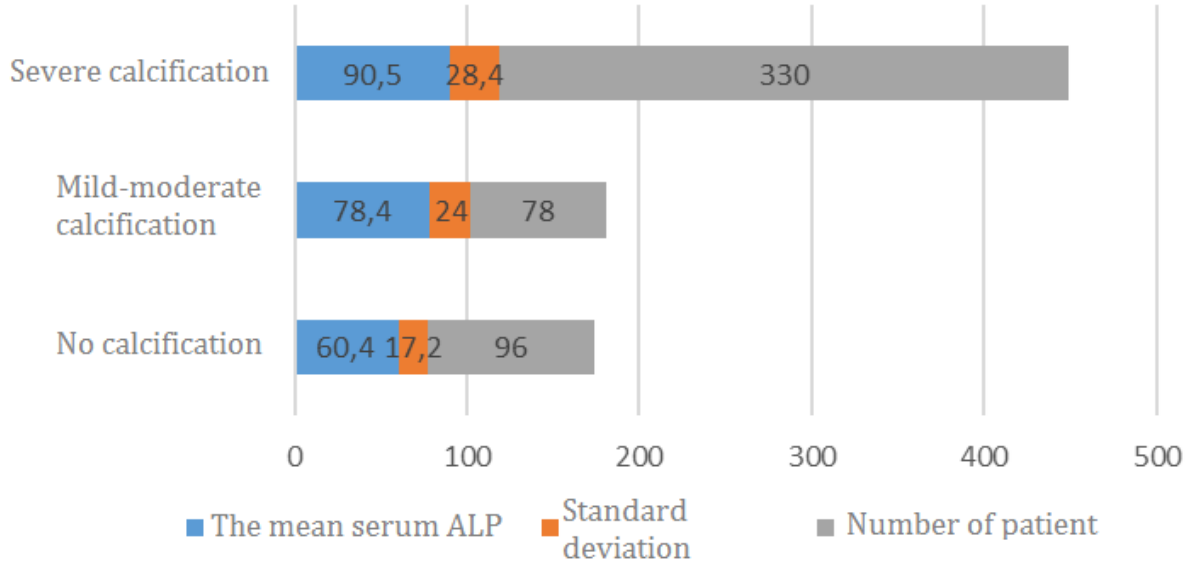

Figure 2. Mean serum ALP, standard deviation, and the number of patients according to the severity of calcification.

DISCUSSION AND CONCLUSION

This study determined the mean serum ALP levels of the group with calcification to be significantly higher than the group without calcification (p=0.000). In addition, those with severe calcifications were found to have a significantly higher mean serum ALP than those with mild-moderate calcification (p=0.001).

Cerebrovascular diseases are one of the leading causes of mortality and morbidity in many developed and developing countries (16). Nevertheless, many studies are investigating the pathophysiology of stroke. Recent literature has particularly focused on vascular calcification (VC). Numerous studies investigating the relationship between VC and stroke have revealed that VC is not just an aging-related process. VC causes ischemia, especially in the arterial wall, and affects many systems.

VC is a pathological process characterized by loss of elasticity and thickening of the artery wall's media and/or intima layers due to mineral deposition (13,17,18). VC promotes arterial stiffness (9,10), which contributes to the development of cerebral ischemia (ischemic stroke, white matter hyperintensity, cerebral microhemorrhages) (19-22).

Due to the widespread use of VC as an indicator of atherosclerosis in previous studies (23), there is an increasing interest in calcification measurement by tomography, which is a non-invasive method. In these studies, lesions above 90 Hounsfield units detected in the intracranial artery wall on non-contrast brain CT were considered IAC. Calcification burden was calculated based on changes in vessel wall and diameter (24-26). Today, some scoring methods (Kockelkoren method) can also distinguish intimal (score<7) and medial (score≥7) calcifications (13,22). In this study, the scoring method mentioned in the "Evaluation of Intracranial Arterial Calcification" section was used without distinguishing between intimal and medial calcifications, in order to facilitate the application in routine practice, not to take much time, and to provide an overview of the relationship between calcification and ALP.

Various pathophysiological mechanisms (such as apoptosis, osteochondrogenic differentiation, elastin degradation, VC activators, and inhibitors) are thought to be involved in VC development processes. ALP plays an activator role in the development of VC. Essentially, ALP is a marker of bone or hepatic diseases (such as vitamin D deficiency, renal osteodystrophy, or cholestasis); however, a small amount is secreted from the intestines, kidneys, and leukocytes. Recently, the role of ALP in vascular diseases has been frequently studied. These studies generally interpreted ALP as an early marker of vascular calcification (27).

ALP contributes to vascular calcification by catalyzing the hydrolysis of inorganic pyrophosphate (1,28). Pyrophosphate in the arterial wall is a potent inhibitor of vascular calcification. However, there is no study revealing the relationship between intracranial arterial calcification and serum ALP levels. Therefore, the present study sought whether there is a relationship between IAC and serum ALP values.

As indicated in the literature, calcification is more common in advanced ages (29). Our study determined the mean age of patients with intracranial arterial calcification to be higher than those without calcification. This finding raises the question of "Is age the main effective factor in the significant relationship determined between calcification and ALP?" In the present study, analysis after excluding the age factor revealed that serum ALP levels were 9-9.5 times higher in patients with intracranial arterial calcification, regardless of age (Mantel-Haenszel Common Odds Ratio Estimate=9.339; p=0.000). However, the regression analysis's evaluation of all risk factors revealed 8.4 times higher ALP elevation in those with calcifications than in those without calcifications. While some previous studies found a relationship between gender and calcification (30), other studies could not show any relationship (31). In the present study, the distribution of men and women in all groups was close to each other (p>0.05).

As mentioned above, ALP plays an activator role in the formation of vascular calcification. Vascular calcification causes narrowing of the vessel diameter and ischemia in the arterial irrigation area. Ultimately, detection of vascular calcification in the intracranial arteries of the brain can be considered to contribute to the development of cerebral ischemic events. In this context, previous studies have also shown that the frequency of intracranial artery calcification is

higher in patients presenting with ischemic stroke clinics (32,33). For example, in a study of 159 patients with acute ischemic stroke, the incidence of intracranial arterial calcification was 86.2% (N=137) (34). In the present study, the incidence of intracranial arterial calcification in patients with cerebrovascular disease was 92% (N=254). This situation can also be interpreted as "As calcification increases, the risk of stroke increases, and as the frequency of stroke increases, the incidence of calcification increases." In conclusion, as also suggested in previous studies, intracranial arterial calcification can be used to predict acute stroke development (35).

Previous studies have shown that arterial calcification is associated with an increased risk of cerebrovascular disease together with traditional stroke risk factors (such as advanced age, diabetes, hypertension, HL) (29,32). The present study revealed a significant correlation between intracranial arterial calcification and other traditional stroke risk factors (previous stroke history, DM, HT) except smoking, HL, CAD, and AF, regardless of gender. Regression analysis further determined that patients with calcification had 3.1 times higher HT frequency, 6.2 times higher DM, three times higher stroke history, and 20.5 times higher age than patients without calcifications. Unlike previous publications, no significant relationship was observed between smoking and calcification due to insufficient smoking records (33).

In line with the previous studies, the present study showed that vascular calcification is more common in patients with CKD (36). In addition, the high mean serum creatinine in patients with vascular calcification in our study also supports this situation. Due to insufficient PTH and vitamin D records, an evaluation could not be made between these two values and calcification. Calcium and phosphorus levels were not significantly different in those with and without calcification ($p>0.05$). This situation can be explained as follows: Previous studies have reported that phosphorus excretion decreases in patients with CKD, and increased serum phosphorus and calcium ions combine to form a calcium-phosphorus product, which underlies the main mechanism responsible for the development of vascular calcification (37-39). This study could not demonstrate the effects of calcium and phosphorus on vascular calcification since not all people in the groups had CKD. There were not enough CKD patients to be evaluated separately.

This study determined that the mean serum ALP was higher in people with stroke risk factors (DM, HT, CAD, CKD, and HL) except smoking, AF, and previous stroke history. The effect of HL on serum ALP levels was not observed when CAD was excluded (OR=1.54; $p=0.60$). Nevertheless, a direct relationship could not be detected between stroke and ALP ($p>0.05$). Some previous studies also could not demonstrate a significant relationship between ALP and cerebral atherosclerosis (40). However, it has been shown that ALP has a significant effect on stroke mortality (41,42). Similarly, no significant association was found between ALP and stroke in this study. However, considering the contribution of ALP to the formation of vascular calcification, ALP can be thought to indirectly increase the risk and mortality of cerebrovascular disease through vascular calcification, although not directly. For this purpose, there is a need for studies that reveal the relationship between stroke and ALP more clearly.

Atherosclerosis is a systemic vascular process (43). Inflammation is critical in the development of atherosclerosis and is reflected by an increase in CRP. As in previous studies (44), the mean serum ALP was higher in the high CRP group ($p<0.001$), and the CRP level was higher in those with calcification (p0.05). This may explain the calcified plaques easily detectable with CT (45,46) in advanced stages of atherosclerosis (43). Albumin, on the other hand, is a negative acute-phase reactant. Its levels decrease in inflammatory processes. This study found albumin values to be lower in patients with calcification. These findings support that inflammation has a significant effect on the development of vascular calcification, as suggested in previous publications (40-42).

The major limitation of our study is the retrospective data collection. Hence, some data (such as smoking and AF) were insufficient. Apart from that, the calculation of the IAC load was subjective, as a single researcher obtained the data. Therefore, it can be thought that this situation may cause bias. In addition, no validation study has been carried out for the method we used. However, the fact that everyone in daily practice can easily apply the method used in this study, the data can be easily interpreted without additional training, and all these processes do not

cause much time loss can be interpreted as the advantages of the study. Moreover, we believe that our study is valuable in giving clinical researchers a general idea about the relationship between IAC and serum ALP levels, which has not been shown in previous studies.

In conclusion, a significant relationship was found between IAC and serum ALP levels in our study. It was also observed that this relationship becomes more pronounced as the IAC burden increases. In addition, it was determined that both intracranial artery calcification and serum ALP levels were higher in people with a high risk of ischemic stroke. Based on these results, it can be said that increased IAC burden and high serum ALP level may be predictors of acute ischemic stroke.

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Ethics

Ethics Committee Approval: The study was approved by Kahramanmaraş Sütçü İmam University Scientific Researches Ethics Committee (Number: 2014/05-14, Date: 12.05.2014).
Informed Consent: The authors declared that informed consent was not obtained from the patients, because the study is retrospective
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