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Original Article

Calcitriol Attenuates the Serum Level of Inflammatory Biomarkers in Ischemic Stroke Patients

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Abstract

Background: Inflammation is considered a highly important factor in the pathophysiology of ischemic stroke. Considering the neuroprotective and anti-inflammatory effects of calcitriol, its administration can be effective in reducing inflammation and ischemic stroke. Thus, this study amid to evaluate the modulatory effects of calcitriol on post-ischemic stroke inflammatory response.

Methods: This retrospective cohort study investigated 41 subjects who were diagnosed with acute ischemic stroke and were admitted to the neurology ward in the first 24 hours after the stroke. The exprimental group was given 1 µg/day calcitriol for 3 consecutive days. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured after taking blood samples immediately upon admission and after 72 hours.

Results: Our results revealed that CPR and ESR values were elevated after an ischemic stroke, while calcitriol could significantly ($P<0.05$) diminish the ESR value after 72 hours.

Conclusion: Probably, due to its anti-inflammatory properties, calcitriol acts as protective reagent to reduce inflammation after ischemic stroke.

Keywords: Calcitriol, Ischemic stroke, Inflammation, CPR, ESR

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Introduction

As an acute neurological injury, stroke is caused by obstructed blood flow due to the blockage or rupture of an artery (1). The second main reason for death is stroke worldwide, which occurs once every 5 seconds (2). Generally, stroke is classified into ischemic and hemorrhagic types (3). As the most common type of stroke (up to 87%), ischemic stroke occurs due to the blood clotting or reduction of oxygen-rich blood supply to the brain (4).

In contrast, hemorrhagic stroke occurs when a blood vessel ruptures or bursts in or around the brain (5). There is another type of stroke that is temporary. It is called "a transient ischaemic attack" (TIA) and is also known as a mini-stroke (6). The symptoms of TIA last for a short time, and it happens because of the temporary blockage or rupture of a vessel in the brain.

Inflammation cascade is immediately activated after the occurrence of cerebral ischemia (7). In this regard, C-reactive protein (CRP) is well-known as one of the best reliable biomarkers of inflammation in humans, rising dramatically due to any type of inflammation (8). Moreover, the erythrocyte sedimentation rate (ESR) or Sed rate is considered a blood test to reveal inflammatory activities in the body and is helpful in the diagnosis or monitoring of the progress of the inflammatory disease (9). Several studies indicated that CRP and ESR values were increased in ischemic stroke patients (9, 10).

Although the non-contrast cranial computed tomography (CT) scan of the head is used for the identification of acute ischemic stroke, magnetic resonance imaging is more sensitive than a CT scan (11). To date, the primary ischemic stroke therapy is the administration of intravenous recombinant tissue plasminogen activator (IV r-tPA) to 4.5 hours (12). However, there is an association between vitamin D serum level and the reduction of stroke risk, and this issue has gained attention in the last decades (13, 14).

As the active form of vitamin D, calcitriol (1,25-dihydroxy vitamin D3) plays a crucial role in regulating calcium and phosphorus homeostasis. In addition, its serum levels are associated with the severity, prognosis, and reduction

of stroke (15). Notably, calcitriol regulates the immune system and production of pro-inflammatory cytokines in the brain by binding to a specific receptor (16, 17). Meta-analysis studies revealed that high serum levels of calcitriol had an anti-flammatory effect on stroke occurrence (18), while low serum levels of calcitriol were associated with a 2.5-fold increase in acute ischemic stroke (19). Moreover, one study investigated the benefits of vitamin D3 supplementation in improving outcomes in ischemic stroke patients (20).

However, this retrospective cohort study aims to evaluate the modulatory effects of calcitriol supplementation in inflammation improvement in ischemic stroke patients.

Materials and Methods

Study Design

This two-center retrospective cohort study assessed the effect of calcitriol supplementation on reducing inflammation biomarkers in ischemic stroke patients admitted to the neurology ward in the first 24 hours after the stroke in Shahid Beheshti Hospital and Farshchian-Sina Hospital (Hamadan, Iran) from May 2021 to September 2022. Ischemic stroke was diagnosed by a specialist based on CT scan imaging. This study was approved by the Ethics Committee of Hamadan University of Medical Sciences (ethical code IR.UMSHA.REC.1397.136).

Inclusion and Exclusion Criteria

Overall, 78 patients were diagnosed with stroke to participate in this study. The inclusion criteria were age above 18 years old, admission within 24 hours of symptom onset, and diagnosed stroke confirmed by the CT scan and magnetic resonance imaging. Patients were excluded if they had chronic intracerebral hemorrhage, were treated with immunosuppressive medicine, showed an unwillingness to participate in the study, suffered from cognitive or behavioral disorders that lead to their non-cooperation, or were pregnant or lactating women.

Data Sampling

Written informed consent was obtained from all participants with the approval by their specialist after a thorough explanation of the study's aims and protocol. Then, demographic, laboratory, and clinical data were gathered from the patient's files and the questionnaire form. A total of 41 patients were selected and randomly divided into the control and intervention groups. The intervention group received 1 µg/day of calcitriol for 3 consecutive days. A blood sample (3 mL) was taken from each patient prior to any treatment (within 24 hours of symptom onset) and again after calcitriol treatment.

C-Reactive Protein and Erythrocyte Sedimentation Rate Assay Methods

To measure CRP and ESR values in patients, the turbidmetric immunoassay of serum CRP was performed using the Mindray BS-800 automated biochemistry analyzer (Shenzhen Mindray Bio-Medical Electronics, China) and the ESR analyzer (ParsianTeb, Iran), respectively. The CRP and ESR results were expressed as µg/mL and mm/hour, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS, version 21.0 (IBM Inc., Armonk, NY, USA). The normality of the variables was checked using the Kolmogorov-Smirnov test. Moreover, continuous and categorical data were expressed as means ± standard deviations (SD), as well as numbers and percentages, respectively. The two groups with normal and non-normal distribution were compared using an independent t-test and Mann-Whitney test, respectively, and $P<0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

Based on the inclusion and exclusion criteria, 41 patients were enrolled in this study. The demographic and clinical characteristics of all patients are reported in Table 1. Changes in age, gender, and comorbidities were not significant ($P<0.05$). The mean age of the control and intervention patients were 67.7 ± 2.28 and 68.9 ± 3.05, respectively. In addition, there were 11 (52.38%) males and 10 (47.61%) females in the control group, as well as 12 (60%) males and 10 (40%) females in the intervention group. The comorbidities results revealed that most male (58.06%) and female (51.72%) patients had hypertension (HTN). The other comorbidities of patients are listed in Table 1.

C-Reactive Protein and Erythrocyte Sedimentation Rate Values

Table 2 presents the CRP and ESR variations in patients. As the best reliable biomarkers of inflammation in humans, CRP value decreased after calcitriol supplementation (1 µg/day) for 72 hours in the intervention group but this reduction was not significant as compared to the control group ($P<0.05$). Moreover, the number of patients who received calcitriol supplementation had a lower ESR value in comparison to the control group ($P<0.05$). However, the mean's differences of CRP and ESR between before treatment and after treatment with calcitriol was

Table 1. Demographic and Clinical Data of the 41 Patients

Categorical Variables	Control (n = 21)	Intervention (n = 20)	*P*-Value
Age (years, mean ± SD)	67.7 ± 2.28	68.9 ± 3.05	>0.05
Gender, N (%)			
Male	11 (52.38)	12 (60)	>0.05
Female	10 (47.61)	8 (40)	
Comorbidities, N (%)			
Hypertension	18 (58.06)	15 (51.72)	
Diabetes	7 (22.58)	4 (13.79)	>0.05
Coronary artery disease	4 (12.9)	6 (20.68)	
Other diseases	2 (6.45)	4 (13.79)	

Note. SD: Standard deviation.

Table 2. CRP and ESR Values of the 41 Patients

Biomarker	Control (n = 21)	Intervention (n = 20)	*P*-Value
CRP (mean ± SD)			
Before treatment	23.81 ± 6.35	28.4 ± 7.44	0.042
After 72 hours of calcitriol treatment	36.86 ± 5.37	23 ± 6.24	0.064
Mean difference	13.05 ± 3.39	-5.4 ± 8.78	0.05
ESR (mean ± SD)			
Before treatment	39.86 ± 6.94	30.50 ± 4.85	0.32
After 72 hours of calcitriol treatment	46 ± 5.75	20.95 ± 3.64	0.008
Mean difference	9.26 ± 0.68	-7.51 ± 9.7	0.04

Note. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SD: Standard deviation.

significant ($P < 0.05$).

Discussion

Our findings demonstrated that ischemic stroke mostly happens in elderly people, and HTN can be one of the important risk factors for the etiology of stroke (21, 22). Notably, the modulatory effects of calcitriol supplementation on inflammation in ischemic stroke patients revealed that calcitriol reduced the CRP and ESR values. However, a few clinical studies have so far evaluated the positive and promising effects of calcitriol supplementation on ischemic stroke outcomes (23).

It has been reported that age and HTN are the two greatest risk factors for ischemic stroke (24, 25). Aging has been accepted to be associated with an increased secretion of pro-inflammatory cytokines, such as interleukin 10 and interleukin 6 (26). Moreover, as a modifiable risk factor, HTN plays a crucial role in increasing the incidence of stroke and worsening the outcomes (27). Additionally, patients with HTN have a larger infraction, blood-brain barrier disruption, vascular wall damage, and more susceptibility to cerebral small vessel diseases, leading to cognitive deficits and lacunar stroke (28, 29).

In this regard, Zhu et al found that the mean age of acute ischemic stroke patients was above 60 years old, 73% of patients were men, and 92.4% of patients had HTN (11). In addition, Wang et al concluded that patients with acute ischemic stroke had a mean age well above 60 years old, and 62.7% of 51 patients had HTN (30). These findings potentially confirmed that the effects of age and HTN are associated with an increase in the incidence of stroke and worsen outcomes.

CRP is highly related to inflammation, and its elevation levels in ischemic stroke are a reliable biomarker in prognosis. The level of CRP in the healthiest adults is less than 0.3 mg/dL, and 1.0–10 mg/dL is related to systemic inflammation (31). Our results confirmed that CRP levels in the control and intervention group were about 2.38 mg/dL and 2.84 mg/dL, respectively, displaying a moderate risk of stroke.

As an indirect biomarker of inflammation, ESR was increased in ischemic stroke patients. The ESR values in healthy men and women is less than 15 (mm/h) and 20 (mm/h), respectively (32). It has been reported that inflammation leads to coagulant activation, and the elevation of the ESR levels can be related to atherosclerosis and lacunar stroke (33).

Based on the Trial of Org 101072 in Acute Stroke Treatment classification, large artery atherosclerosis is the main mechanisms of ischemic stroke (34). In this study, it seems that the CRP and ESR levels elevation may be due to the increased frequency of large-artery atherosclerosis in ischemic stroke patients. Similarly, several clinical studies indicated that the CRP and ESR values increased in ischemic stroke patients (35-37).

Calcitriol supplementation for three consecutive days at 1 μg/kg led to a decrease in the CRP and ESR values, but this decline was only significant at the ESR level in the intervention group. Several studies showed that calcitriol has neuroprotective, antioxidant, anti-inflammatory, anti-apoptotic, and anticoagulant properties (38, 39). It has been reported that most ischemic stroke patient has vitamin D3 insufficiency (40). Hence, treating vitamin D3 deficiency or insufficiency can reduce the risk of stroke (41).

Although the exact molecular mechanism of calcitriol modulatory effects in ischemic stroke has not been fully elucidated, the possible neuroprotective effects of calcitriol in ischemic stroke are the reduction of glutamate release, reduction of pro-inflammatory cytokines and chemokines, improvement of antioxidant defense system (e.g., superoxide dismutase, glutathione peroxidase), and up-regulation of neurotropic factors (42-45). Therefore, the reduction of inflammatory cytokines production leads to the attenuation of CRP and ESR values after calcitriol supplementation.

This study had some limitations, such as the small number of participants and measurement of the serum levels of vitamin D. In addition, due to financial constrictions, it was impossible to assess pro-inflammatory cytokines. Therefore, it is recommended that further studies evaluate the serum level of vitamin D and pro-inflammatory cytokines. Despite these limitations, our results confirmed a positive association between calcitriol supplementation and reduction of inflammation in patients with ischemic stroke.

Conclusion

Overall, evaluating the effects of calcitriol supplementation on the serum level of inflammatory biomarkers in three days revealed that calcitriol has a positive effect on the treatment of stroke through its neuroprotective and anti-inflammatory effects, which was proven by the reduction of inflammatory factors ESR and CRP. However, calcitriol can be recommended as a therapeutic reagent for preventing or treating ischemic stroke.

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Competing Interests

The authors declared that they have no conflict of interests.

References

1. van der Worp HB, van Gijn J. Clinical practice. Acute ischemic stroke. N Engl J Med 2007;357(6):572-9. doi:10.1056/NEJMcp072057
2. Katan M, Luft A. Global burden of stroke. Semin Neurol 2018;38(2):208-11. doi:10.1055/s-0038-1649503
3. Jiang S, Li T, Ji T, Yi W, Yang Z, Wang S, et al. AMPK: potential therapeutic target for ischemic stroke. Theranostics 2018;8(16):4535-51. doi:10.7150/thno.25674
4. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). Cerebrovasc Dis 2013;36(1):1-5. doi:10.1159/000352050
5. Esmael A, El Sherif M, Saad M. Prediction of 30-days mortality of intracerebral hemorrhage by a powerful but easy to use intracerebral hemorrhage score. Int Neuropsychiatr Dis J 2016;6(2):1-11. doi:10.9734/INDJ/2016/22414
6. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007;6(12):1063-72. doi:10.1016/s1474-4422(07)70274-0
7. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med 2011;17(7):796-808. doi:10.1038/nm.2399
8. Sheriff A, Kayser S, Brunner P, Vogt B. C-reactive protein triggers cell death in ischemic cells. Front Immunol 2021;12:630430. doi:10.3389/fimmu.2021.630430
9. Singh AS, Atam V, Yathish BE, Das L, Koonwar S. Role of erythrocyte sedimentation rate in ischemic stroke as an inflammatory marker of carotid atherosclerosis. J Neurosci Rural Pract 2014;5(1):40-5. doi:10.4103/0976-3147.127870
10. VanGilder RL, Davidov DM, Stinehart KR, Huber JD, Turner RC, Wilson KS, et al. C-reactive protein and long-term ischemic stroke prognosis. J Clin Neurosci 2014;21(4):547-53. doi:10.1016/j.jocn.2013.06.015
11. Zhu X, Ding J, Wang B, Wang J, Xu M. Circular RNA DLGAP4 is down-regulated and negatively correlates with severity, inflammatory cytokine expression and pro-inflammatory gene miR-143 expression in acute ischemic stroke patients. Int J Clin Exp Pathol 2019;12(3):941-8.
12. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359(13):1317-29. doi:10.1056/NEJMoa0804656
13. Yarlagadda K, Ma N, Doré S. Vitamin D and stroke: effects on incidence, severity, and outcome and the potential benefits of supplementation. Front Neurol 2020;11:384. doi:10.3389/fneur.2020.00384
14. Park KY, Chung PW, Kim YB, Moon HS, Suh BC, Won YS, et al. Serum vitamin D status as a predictor of prognosis in patients with acute ischemic stroke. Cerebrovasc Dis 2015;40(1-2):73-80. doi:10.1159/000434691
15. Marek K, Cichoń N, Saluk-Bijak J, Bijak M, Miller E. The role of vitamin D in stroke prevention and the effects of its supplementation for post-stroke rehabilitation: a narrative review. Nutrients 2022;14(13):2761. doi:10.3390/nu14132761
16. Peterlik M, Cross HS. Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. Eur J Clin Nutr 2009;63(12):1377-86. doi:10.1038/ejcn.2009.105
17. Dobbels B, Mertens G, Gilles A, Moyaert J, van de Berg R, Fransen E, et al. The virtual morris water task in 64 patients with bilateral vestibulopathy and the impact of hearing status. Front Neurol 2020;11:710. doi:10.3389/fneur.2020.00710
18. Leung RY, Han Y, Sing CW, Cheung BM, Wong IC, Tan KC, et al. Serum 25-hydroxyvitamin D and the risk of stroke in Hong Kong Chinese. Thromb Haemost 2017;117(1):158-63. doi:10.1160/th16-07-0551
19. Li L, Lietz G, Bal W, Watson A, Morfey B, Seal C. Effects of quinoa (*Chenopodium quinoa* Willd.) consumption on markers of CVD risk. Nutrients 2018;10(6):777. doi:10.3390/nu10060777
20. Atif F, Yousuf S, Espinosa-Garcia C, Harris WAC, Stein DG. Post-ischemic stroke systemic inflammation: Immunomodulation by progesterone and vitamin D hormone. Neuropharmacology 2020;181:108327. doi:10.1016/j.neuropharm.2020.108327
21. Aiyagari V, Gorelick PB. Hypertension and Stroke: Pathophysiology and Management. Springer; 2016.
22. Mikdashi J, Handwerger B, Langenberg P, Miller M, Kittner S. Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. Stroke 2007;38(2):281-5. doi:10.1161/01.Str.0000254476.05620.14
23. Kim C, Lee SH, Lim JS, Kim Y, Jang MU, Oh MS, et al. Impact of 25-hydroxyvitamin D on the prognosis of acute ischemic stroke: machine learning approach. Front Neurol 2020;11:37. doi:10.3389/fneur.2020.00037
24. Lucke-Wold BP, Turner RC, Lucke-Wold AN, Rosen CL, Huber JD. Age and the metabolic syndrome as risk factors for ischemic stroke: improving preclinical models of ischemic stroke. Yale J Biol Med 2012;85(4):523-39.
25. Gorgui J, Gorshkov M, Khan N, Daskalopoulou SS. Hypertension as a risk factor for ischemic stroke in women. Can J Cardiol 2014;30(7):774-82. doi:10.1016/j.cjca.2014.01.007
26. Hein AM, O'Banion MK. Neuroinflammation and cognitive dysfunction in chronic disease and aging. J Neuroimmune Pharmacol 2012;7(1):3-6. doi:10.1007/s11481-011-9340-1
27. Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: impact of hypertension on the cerebral circulation. J Cereb Blood Flow Metab 2018;38(12):2129-49. doi:10.1177/0271678x18800589
28. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33(5):1315-20. doi:10.1161/01.str.0000014509.11540.66
29. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke 2009;40(7):2442-9. doi:10.1161/strokeaha.109.548602
30. Wang L, Zhao XM, Wang FY, Wu JC, Wang Y. Effect of vitamin D supplementation on the prognosis of post-stroke fatigue: a retrospective cohort study. Front Neurol 2021;12:690969. doi:10.3389/fneur.2021.690969
31. Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. J Periodontol 2008;79(8 Suppl):1544-51. doi:10.1902/jop.2008.080249
32. Pisetsky DS. Laboratory testing in the rheumatic diseases. In: Goldman's Cecil Medicine. Elsevier; 2012. p. 1651-6.
33. Alvarez-Perez FJ, Castelo-Branco M, Alvarez-Sabin J. Usefulness of measurement of fibrinogen, D-dimer, D-dimer/fibrinogen ratio, C reactive protein and erythrocyte sedimentation rate to assess the pathophysiology and mechanism of ischaemic stroke. J Neurol Neurosurg Psychiatry 2011;82(9):986-92. doi:10.1136/jnnp.2010.230870
34. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24(1):35-41. doi:10.1161/01.str.24.1.35
35. Aliasghari F, Izadi A, Khalili M, Farhoudi M, Ahmadiyan S, Deljavan R. Impact of premorbid malnutrition and dysphagia on ischemic stroke outcome in elderly patients: a community-based study. J Am Coll Nutr 2019;38(4):318-26. doi:10.1080/07315724.2018.1510348

36. Seystahl K, Schweizer J, Katan M, Weber SJ, Hug A, Wanner M, et al. Stroke-associated infections in patients with and without cancer. Neurooncol Pract 2023;10(2):176-85. doi:10.1093/nop/npac075
37. Elhfnawy AM, Elsalamawy D, Abdelraouf M, Schliesser M, Volkmann J, Fluri F. Red flags for a concomitant giant cell arteritis in patients with vertebrobasilar stroke: a cross-sectional study and systematic review. Acta Neurol Belg 2020;120(6):1389-98. doi:10.1007/s13760-020-01344-z
38. Evans MA, Kim HA, Ling YH, Uong S, Vinh A, De Silva TM, et al. Vitamin D3 supplementation reduces subsequent brain injury and inflammation associated with ischemic stroke. Neuromolecular Med 2018;20(1):147-59. doi:10.1007/s12017-018-8484-z
39. Mohd S, Sharma S, Mishra A, Ashraf MZ. Vitamin D and its relationship with the pathways related to thrombosis and various diseases. In: Özdemir Ö, ed. Vitamin D. IntechOpen; 2021. doi:10.5772/intechopen.97299
40. Wajda J, Świat M, Owczarek AJ, Brzozowska A, Olszanecka-Glinianowicz M, Chudek J. Severity of vitamin D deficiency predicts mortality in ischemic stroke patients. Dis Markers 2019;2019:3652894. doi:10.1155/2019/3652894
41. Hervella P, Alonso-Alonso ML, Pérez-Mato M, Rodríguez-Yáñez M, Arias-Rivas S, López-Dequidt I, et al. Surrogate biomarkers of outcome for wake-up ischemic stroke. BMC Neurol 2022;22(1):215. doi:10.1186/s12883-022-02740-z
42. Lasoń W, Jantas D, Leśkiewicz M, Regulska M, Basta-Kaim A. Vitamin D3 and ischemic stroke: a narrative review. Antioxidants (Basel) 2022;11(11):2120. doi:10.3390/antiox11112120
43. Pertile RAN, Cui X, Hammond L, Eyles DW. Vitamin D regulation of GDNF/Ret signaling in dopaminergic neurons. FASEB J 2018;32(2):819-28. doi:10.1096/fj.201700713R
44. Chen KB, Lin AM, Chiu TH. Systemic vitamin D3 attenuated oxidative injuries in the locus coeruleus of rat brain. Ann N Y Acad Sci 2003;993:313-24. doi:10.1111/j.1749-6632.2003.tb07539.x
45. Bikle DD, Schwartz J. Vitamin D binding protein, total and free vitamin D levels in different physiological and pathophysiological conditions. Front Endocrinol (Lausanne) 2019;10:317. doi:10.3389/fendo.2019.00317