Clinico-radiological correlation between serum calcium and acute ischemic stroke

Gaurav M Kasundra, Isha Sood¹, Bharat Bhushan, Gopal Kishan Bohra¹, PS Supriya¹

Departments of Neurology and ¹Medicine, Dr. Sampurnanand Medical College, Jodhpur, Rajasthan, India

ABSTRACT

Background: Ischemic injury in stroke leads to intracellular calcium accumulation, which activates the enzyme cascade causing cell death. Aims: To determine the correlation between serum calcium (Ca) and albumin-corrected calcium (CCa) levels with acute ischemic stroke (AIS) for short-term outcome and infarct size (IS). Methods: An observational study was carried out in 50 patients in a tertiary care hospital in India over 2 years (from December 2008 to December 2010). Patients presenting within 72 h of stroke onset and aged ≥40 years were included. Ca was measured, CCa calculated, and head computed tomography (CT) scan was done. National Institute of Health Stroke Scale (NIHSS) was calculated on admission and after 1 week, and Barthel Index (BI) was calculated at 1 week. Pearson’s correlation coefficient was calculated between NIHSS, BI, and IS with both, Ca and CCa. Also, subgroup analysis was done in lacunar, lobar, anterior circulation, posterior circulation, unilateral, and bilateral stroke subgroups. Results: Ca had a significant correlation with NIHSS, BI, and IS (all patients), with BI in lacunar and unilateral strokes and both NIHSS (admission) and BI in lobar, anterior circulation, and bilateral strokes. CCa had a significant correlation with IS and with BI in all patients and in anterior circulation strokes. NIHSS (admission) and BI had a significant correlation with IS. Conclusions: Higher Ca (CCa in some subgroups) is associated with better prognosis and recovery after AIS (except in posterior circulation strokes), and higher Ca and CCa are both associated with smaller IS.

Key words: Acute ischemic stroke, albumin-corrected calcium, Barthel Index, calcium, infarct, infarct size, National Institute of Health Stroke Scale score, prognosis

INTRODUCTION

Cerebrovascular diseases include some of the most common and devastating disorders: ischemic strokes, hemorrhagic stroke, and cerebrovascular anomalies such as intracranial aneurysm and cerebrovascular malformations. The incidence of cerebrovascular disease increases with age and the number of projected scores also increases with increasing age. Major risk factors associated are hypertension, hyperglycemia, tobacco use, and low hemoglobin levels. Association with newer risk factors like homocysteine, high-sensitivity C-reactive protein (hs-CRP), uric acid, and others is also known. Among the newer ones are serum levels of albumin and calcium. Serum calcium levels have a significant role in the molecular pathways of ischemic neuronal death and damage.¹,² Reduction of cerebral blood flow (CBF) below 10-12 ml/100 g/min causes infarction, almost regardless of its duration. A CBF of 6-8 ml/100 g/min causes marked ATP depletion, increase in extracellular K, increase in intracellular Ca, and cellular acidosis, invariably leading to histologic signs of necrosis. These changes do not become apparent for several hours. Free fatty acids (appearing as phospholipases) are activated and destroy the phospholipids of neuronal membranes.

Access this article online

Quick Response Code:

Website: www.ijamhrjournal.org

DOI: 10.4103/2349-4220.148006

Address for correspondence: Dr. Gaurav M Kasundra, 122, Subhash Nagar, Near Preksha Hospital, Pal Road, Jodhpur - 342 008, Rajasthan, India. E-mail: gauravkasundra@gmail.com
Prostaglandins, leukotrienes, and free radicals accumulate, and intracellular proteins and enzymes are denatured. Some current attempts at therapy, for example, are directed at limiting the extent of infarction by blocking the glutamate receptor, particularly \( N \)-methyl-\( d \)-aspartate (NMDA) channel, one of several calcium channels that open under the conditions of ischemia and are set in motion a cascade of cellular events eventuating in neuronal death (apoptosis). However, even complete blockade of the NMDA channels does not prevent cellular death, presumably because dysfunction of several other types of calcium channels continues and allows calcium entry to cells. However, an underlying role of movement of calcium from the extracellular to the intracellular compartment leading to triggering of the cascade of events that eventually lead to neuronal cell death is undeniable. The results of Hong et al.\(^{[3]}\) in experimental studies on rats indicate that ischemic stroke is preventable by dantrolene through reduction of ionized calcium and increase of cyclic adenosine monophosphate (cAMP), thus proving the role of calcium in stroke prognosis. Serum calcium also correlates with the size of cerebral infarct as shown by Buck et al.\(^{[4]}\) Also, the role of cerebral ischemia leading to cerebral edema and eventually a poorer prognosis is well established. We intend to study the significance of serum total calcium and serum-corrected calcium levels in predicting immediate and short-term prognosis in acute ischemic stroke (AIS) as also their correlation with infarct size (IS).

**METHODS**

This was prospective cohort observational study conducted in 50 patients at a tertiary care center government hospital in Baroda, India. The study period was 2 years (from December 2008 to December 2010). Fifty cases of acute ischemic cerebrovascular accidents were studied after screening 108 cases who presented with all vascular events (including hemorrhagic strokes, ischemic strokes, venous sinus thrombosis, and subarachnoid hemorrhage, irrespective of the interval between the onset and presentation to our hospital). Consent of the patients or their next of kin and approval of the institutional review board were taken.

Patients aged \( \geq 40 \) years and diagnosed as having acute ischemic cerebrovascular stroke within previous 72 h by clinical examination and confirmed by a computed tomography (CT) scan were included. Patients aged \( < 40 \) years, presenting with hemorrhagic stroke, subarachnoid hemorrhage, cerebral venous sinus thrombosis, those presenting with ischemic stroke after 72 h of onset, and those with renal or hepatic failure (both of which may affect either the calcium or albumin level and thus alter the results) were excluded from study.

Detailed history was taken and examination of the patients included in the study was done. The National Institute of Health Stroke Scale (NIHSS) score of all the patients at admission was calculated. After 1 week of initial assessment, NIHSS score and Barthel Index (BI; which tests the functional independence objectively) of all patients were calculated. All routine investigations including complete hemogram, fasting sugar, renal function test, liver function test, lipid profile and serum proteins with calcium (Ca), electrocardiogram (ECG), fundus examination, brain CT, chest skiagram, echocardiography, and abdominal ultrasonography (in certain cases) were done. Albumin-corrected calcium (CCa) level was calculated as the sum of serum total calcium level and 0.8 times the difference between normal population albumin level (4 mg/dl) and patient’s albumin level.

CT imaging was performed with a high-speed advantage helical CT scanner (GE Medical Systems) in all patients (mean latency time of doing CT scan was 52.92 ± 14.16 h after the onset of stroke). Radiologically, the subjects were dichotomized among the subgroups of lacunar, lobar, anterior circulation, posterior circulation, unilateral and bilateral strokes. For analysis, the largest lesion slice was selected. The longest lesion axis on this slice was measured with the ruler tool. A second line was drawn perpendicular to the first at the widest dimension. These two measurements were called the \( x \) \((A) \) and \( y \) \((B) \) axes. A third axis, the \( z \) \((C) \) axis, was computed by multiplying the number of slices by slice thickness. The scan slice for CT was 5 mm. Final IS was measured as \( ABC/2 \). This formula was shown as the most accurate one for calculating IS by Sims et al.\(^{[5]}\)

**Statistical analysis**

For statistical analysis, the data were entered in Microsoft Excel format and analyzed using StataCorp USA Version 11.1 and Statistical Package for the Social Sciences software (SPSS, IBM version 16.0). Data were expressed in mean, percentage, and standard deviation. Pearson’s correlation coefficient was used for comparing both Ca and CCa with NIHSS, BI, and IS, and among the subgroups of lacunar, lobar, anterior circulation, posterior circulation, unilateral and bilateral strokes.

**RESULTS**

Mean age of the study population \((N = 50)\) was 59.98 ± 10.3 years (range 45-90). Mean age of male patients \((n = 29)\) was 58.9 ± 9.5 years (range 45-84) and that of female patients \((n = 21)\) was 61.48 ± 11.3 years (range 45-90). Mean latency of presentation from the stroke onset was 47.48 ± 13.7 h (range 20-68) and mean latency for
getting the CT scan done after the stroke onset was 52.92 ± 14.16 h (range 22-72). Mean IS on CT was 53.48 ± 24.5 cm³ (range 16-102). Mean Ca, albumin, and CCa were 9.17 ± 0.8 mg/dl (range 7.1-10.9), 3.8 ± 0.7 mg/dl (range 2.1-5.0), and 9.47 ± 0.78 mg/dl (range 7.58-11.14), respectively. Mean NIHSS scores on admission and after 1 week were 10.64 ± 7.9 (range 2-31) and 8.92 ± 7.9 (range 0-28), respectively. Mean change in NIHSS score was 1.72 ± 1.4 (range 0-6). Mean BI at 1 week was 57.2 ± 37.5 (range 0-100). The most common presenting complaint was right hemiparesis in 44% of patients. The risk factors most commonly detected were a past history of hypertension, stroke, and smoking in self, as well as a family history of hypertension. Rest of the baseline characteristics are as detailed in Table 1.

Serum Ca had a significant correlation with NIHSS at admission, NIHSS after 1 week, change in NIHSS, BI, and IS (r-values: −0.3915, −0.4473, 0.2986, 0.5267, and −0.4256, respectively) in all patients [Figure 1]. Among the subgroups analyzed, calcium had significant correlation with BI in lacunar and unilateral strokes and with both NIHSS and BI in lobar, anterior circulation, and bilateral strokes [Figure 2]. CCa had a significant correlation only with BI and IS (r-values: 0.3206 and −0.356, respectively) and not with any of the NIHSS scores measured when all patients were analyzed. Among the subgroups, CCa had a significant correlation only with BI in anterior circulation strokes and none of the others [Figure 3]. Details of the same, including the r-values and P-values are as in Table 2. Both NIHSS and BI had a highly significant correlation with IS (P = 0.0001 and P = 0.0002, respectively). Correlation of IS with Ca, CCa, NIHSS at admission, and BI is illustrated in Figure 4.

Table 1: Demographic profile and baseline characteristics of the study population

| Characteristic                      | Value               |
|------------------------------------|---------------------|
| Mean age (years)                   | 59.98±10.3          |
| Males (n=29) mean age (years)      | 58.9±9.5            |
| Females (n=21) mean age (years)    | 61.48±11.3          |
| Mean time of presentation to hospital after stroke onset (h) | 47.48±13.7          |
| Mean time of doing CT scan after stroke onset (h) | 52.92±14.16         |
| Mean infarct size on CT (cm³)      | 53.48±24.5          |
| Mean NIHSS score on admission      | 10.64±7.9           |
| Mean NIHSS score after 1 week      | 8.92±7.9            |
| Mean change in NIHSS score         | 1.72±1.4            |
| Mean Barthel index score after 1 week | 57.2±37.5          |
| Mean serum calcium (Ca) level on admission (mg/dl) | 9.17±0.8           |
| Mean albumin level on admission (mg/dl) | 3.8±0.7            |
| Mean albumin-corrected calcium (CCa) level on admission (mg/dl) | 9.47±0.7       |
| Motor weakness                     |                     |
| Right hemiplegia                   | 44%                 |
| Left hemiplegia                    | 30%                 |
| Bilateral hemiplegia               | 10%                 |
| Right upper limb monoplegia        | 10%                 |
| No motor weakness                  | 6%                  |
| Past medical history               |                     |
| Stroke/transient ischemic attack   | 14%                 |
| Diabetes mellitus                  | 8%                  |
| Hypertension                       | 32%                 |
| Ischemic heart disease             | 4%                  |
| Family history                     |                     |
| Stroke                             | 2%                  |
| Diabetes mellitus                  | 6%                  |
| Hypertension                       | 12%                 |
| Ischemic heart disease             | 2%                  |
| Addictions                         |                     |
| Alcoholism                         | 10%                 |
| Tobacco smoking                    | 14%                 |
| Fundus examination                 |                     |
| Hypertensive retinopathy           | 16%                 |
| Diabetic retinopathy               | 6%                  |
| Electrocardiogram                  |                     |
| Ischemic heart disease             | 14%                 |
| Left ventricular hypertrophy       | 24%                 |
| Stroke-related changes             | 20%                 |
| Normal                             | 52%                 |
| Serum lipids: Total cholesterol    | 155.42±40.11        |
| LDL cholesterol                    | 146±20.72           |

NIHSS = National Institute of Health Stroke Scale, LDL = Low density lipoprotein
DISCUSSION

AIS occurs whenever the CBF falls below the critical level and, thus cellular hypoxia occurs. The subsequent failure of the cellular homeostatic functions leads to calcium influx. Calcium ions move from the serum to the neurons primarily via the choroid plexus as shown in animal studies. This leads to lipid peroxidation due to the enzyme cascade activation and further increase in the movement of calcium from extracellular to intracellular compartment due to creation of calcium sink. Although calcium from the extracellular compartment moves to

Table 2: Pearson’s correlation between calcium and corrected calcium with various groups and subgroups of population

| Parameters                        | Calcium |                  | Albumin corrected calcium |                  |
|-----------------------------------|---------|-------------------|---------------------------|-------------------|
|                                   | r-value | P-value            | r-value                   | P-value            |
| All strokes: Admission NIHSS score| −0.3915 | 0.0048 (S)        | −0.1785                   | 0.2135 (NS)        |
| All strokes: NIHSS score after 1 week| −0.4473 | 0.0011 (S)        | −0.2258                   | 0.1145 (NS)        |
| All strokes: Change in NIHSS score| 0.2986  | 0.0352 (S)        | 0.2588                    | 0.0696 (NS)        |
| All strokes: Barthel Index after 1 week| 0.5267  | 0.0001 (HS)       | 0.3206                    | 0.0232 (S)         |
| All strokes: Infarct size          | −0.4256 | 0.00203 (S)       | −0.356                    | 0.0111 (S)         |
| Lacunar stroke NIHSS score         | −0.2088 | 0.295 (NS)        | −0.016                    | 0.936 (NS)         |
| Lacunar stroke Barthel Index       | 0.5067  | 0.0069 (S)        | 0.3324                    | 0.09 (NS)          |
| Lobar stroke NIHSS score           | −0.5511 | 0.0064 (S)        | −0.3166                   | 0.141 (NS)         |
| Lobar stroke Barthel Index         | 0.5582  | 0.0056 (S)        | 0.3239                    | 0.131 (NS)         |
| Anterior circulation stroke NIHSS score | −0.4406 | 0.0035 (S) | −0.221                    | 0.159 (NS)         |
| Anterior circulation stroke Barthel Index | 0.5526  | 0.00014 (HS) | 0.3321                    | 0.0316 (S)         |
| Posterior circulation stroke NIHSS score | −0.381 | 0.198 (NS) | −0.1837                   | 0.547 (NS)         |
| Posterior circulation stroke Barthel Index | 0.5365  | 0.058 (NS) | 0.3727                    | 0.209 (NS)         |
| Unilateral stroke NIHSS score      | −0.3329 | 0.062 (NS)        | −0.1331                   | 0.468 (NS)         |
| Unilateral stroke Barthel Index    | 0.4995  | 0.0036 (S)        | 0.3074                    | 0.08 (NS)          |
| Bilateral stroke NIHSS score       | −0.484  | 0.041 (S)         | −0.2579                   | 0.301 (NS)         |
| Bilateral stroke Barthel Index     | 0.5595  | 0.0157 (S)        | 0.3373                    | 0.171 (NS)         |

NIHSS = National Institute of Health Stroke Scale, S = Statistically significant (P < 0.05), HS = Statistically highly significant (P < 0.001), NS = Statistically not significant (P > 0.05)
the intracellular compartment, the degree of rise in intracellular calcium is much more than the drop in extracellular levels.\textsuperscript{[6]} Yet, most studies in animals as well as in humans have shown a positive correlation between extracellular calcium level and better prognosis.\textsuperscript{[7-10]} D’Erasmo et al.\textsuperscript{[10]} found the level of calcium in ischemic stroke patients to be significantly less than that in control population and in patients with transient ischemic attacks.\textsuperscript{[10]} We found a statistically significant ($P < 0.05$) correlation of IS with both calcium level and corrected calcium level. This is in concordance with the findings of Buch et al.\textsuperscript{[4]} and D’Erasmo et al.\textsuperscript{[10]} The highly significant correlation of NIHSS and BI with IS can be logically understood as large infarcts tend to have greater neurological deficits and have a poorer prognosis for early recovery, especially so due to the associated cerebral edema and greater volume of cellular necrosis.

In all the patient groups, as also in the anterior circulation stroke subgroup, Ca had significant ($P < 0.05$) correlation with NIHSS (admission) and highly significant ($P < 0.001$) correlation with BI. Among all patients, the correlation of Ca with NIHSS was stronger after 1 week ($r$-value: $-0.4473$; $P$-value: $0.0011$) than at admission ($r$-value: $-0.3915$; $P$-value: $0.0048$). Also, the change in NIHSS score was significant ($r$-value: $0.2986$). Thus, not only do NIHSS scores on admission and after 1 week correlate with Ca levels, but also the change in the NIHSS score had a significant correlation. This implies that higher Ca levels are associated with a better functional recovery.

In the lacunar stroke and unilateral stroke subgroups, only BI correlated ($P < 0.05$), while NIHSS had a non-significant correlation. Both lobar and bilateral strokes had a significant ($P < 0.05$) correlation with Ca. This might be due to the fact that NIHSS scores measured at the time of admission were affected by other factors. At the time of acute stroke, it would have induced not just the neurological deficits, but also the associated altered mental status, the rapidly recovering aphasia in some patients, as also the psychosocial issues. However, by 1 week when the BI and repeat NIHSS were calculated, the neurological deficits had stabilized and patients had begun partially recovering. Thus, Ca levels correlate better with the 1 week functional outcome than with the admission neurological status. Also, as most of our patients had presented after a delay of almost 48 h or more, the calcium levels that we measured were similar to the “delayed calcium” group of Ovbiagele et al.,\textsuperscript{[1]} which they found to correlate with the recovery at 3 months. Our study thus adds to the knowledge that the improvement shown by Ovbiagele et al.\textsuperscript{[1]} may begin as early as 1 week and may further continue up to 3 months, as in their conclusions.

Also, we found the calcium levels to have a better correlation, compared to the corrected calcium level. CCa had a significant ($P < 0.05$) correlation only with BI among all patients and the anterior circulation stroke subgroups and none of the other stroke subgroups or with NIHSS in any of the groups or subgroups analyzed. As against that, Ca had a statistically significant correlation with many of the subgroups as mentioned above. This is in sync with the findings of Ovbiagele et al.\textsuperscript{[1]} and D’Erasmo et al.\textsuperscript{[10]} The reason for the same has not been found out yet. The correlation of albumin with stroke outcome has been shown to be significant by some and nonsignificant by others.\textsuperscript{[11-16]} However, it is beyond doubt that the albumin levels themselves undergo fluctuations in the acute stages of stroke. Thus, if we are to calculate the corrected calcium level based on the albumin level which itself is unstable, we are bound to
get erroneous results. We propose that this might be the reason why most of the studies till date have failed to find a significant correlation of stroke outcome with CCa levels.

Neither Ca nor CCa in the posterior circulation strokes had a statistically significant correlation with either IS or with NIHSS and BI scores. This may be due to the infarct-associated cerebral edema causing raised intracranial tension playing a major role in the patients’ prognosis and clinical outcome.

One of the limitations of our study was its small sample size. Also, serum calcium level was measured only once, unlike its estimation done multiple times by Ovbiagele et al.[1] Patients were included up to 72 h of onset, while previous studies have shown that serum calcium levels fluctuate quite significantly in the initial hours following stroke. Also, the serum calcium and albumin levels were measured on admission, without any fixed time interval from the onset of the stroke. Thus, this may lead to a bias in the analysis due to lack of standardization of the timing of blood sampling. However, as there have been very few studies of correlation between the calcium levels and prognosis of stroke, this study adds to the available knowledge and proves calcium levels to be a strong contender as a prognostic marker of early recovery and disability.

CONCLUSIONS

Serum calcium level, and not albumin-corrected calcium level, has a significant positive correlation with early (1 week post-stroke) recovery after ischemic stroke (except in posterior circulation strokes).

REFERENCES

1. Ovbiagele B, Starkman S, Teal P, Lyden P, Kaste M, Davis SM, et al.; VISTA Investigators. Serum calcium as prognosticator in ischemic stroke. Stroke 2008;39:2231-6.
2. Siesjo BK, Zhao Q, Pahlmark K, Siesjo P, Katsura K, Folbergrová J. Glutamate, calcium, and free radicals as mediators of ischemic brain damage. Ann Thorac Surg 1995;59:1316-20.
3. Hong SJ, Chioe GC. Effects of intracellular calcium reduction by dantrolene on prevention/treatment of ischemic stroke. J Cardiovasc Pharmacol Ther 1998;3:299-304.
4. Buck BH, Liebeskind DS, Saver JL, Bang OY, Starkman S, Ali LK, et al. Association of higher serum calcium levels with smaller infarct volumes in acute ischemic stroke. Arch Neurol 2007;64:1287-91.
5. Sims JR, Gharai LR, Schafer PW, Vangel M, Rossenthal ES, Lev MH, et al. ABC/2 for rapid clinical estimate of infarct, perfusion, and mismatch volumes. Neurology 2009;72:2104-10.
6. Kristian T, Siesjo BK. Calcium in ischemic cell death. Stroke 1998;29:705-18.
7. Giri S, Agarwal MP, Sharma V. Correlation of serum calcium levels with neurologic severity and short-term outcome in acute ischemic stroke. J Assoc Physicians India 2009;74:112.
8. Guven H, Culliner AE, Koker C, Sarikaya SA, Comoglu SS. Association of serum calcium levels with clinical severity of acute ischemic stroke. Acta Neurol Belg 2011;111:45-9.
9. Appel SA, Molshatzki N, Schwammenthal Y, Merzelik O, Toashi M, Sela BA, et al. Serum calcium levels and long-term mortality in patients with acute stroke. Cerebrovasc Dis 2011;31:93-9.
10. D’Erasmo E, Pisani D, Romagnoli S, Ragno A, Acca M. Acute serum calcium changes in transient ischemic attack and cerebral infarction. J Med 1998;29:311-7.
11. Cho YM, Choi IS, Biao RX, Kim JH, Han JY, Lee SG. Serum albumin at admission for prediction of functional outcome in ischaemic stroke patients. Neuro Sci 2008;29:445-9.
12. Idicula TT, Waje-Andreassen U, Brogger J, Naess H, Thomassen L. Serum albumin in ischemic stroke patients: The higher the better. The bergen stroke study. Cerebrovasc Dis 2009;28:13-7.
13. Dziedzic T, Pera J, Slowik A, Gryz-Kurek EA, Szczudlik A. Hypoalbuminemia in acute ischemic stroke patients: Frequency and correlates. Eur J Clin Nutr 2007;61:1318-22.
14. Dziedzic T, Slowik A, Szczudlik A. Serum albumin level as a predictor of ischemic stroke outcome. Stroke 2004;35:e156-8.
15. Ginsberg MD, Palesch YY, Hill MD, Martin RH, Moy CS, Barson WG, et al.; ALIAS and Neurological Emergencies Treatment Trials (NETT) Investigators. High-dose albumin treatment for acute ischaemic stroke (ALIAS) part 2: A randomised, double-blind, phase-3, placebo-controlled trial. Lancet Neurol 2013;12:1049-58.
16. Kasundra G, Sood I. Prognostic significance of serum albumin levels in acute ischemic stroke. Natl J Integr Res Med 2014;5:1-4.