

# Correlation of Serum Calcium Levels with Severity of Acute Ischaemic Stroke.

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## Abstract

**Background:** Stroke is one of the leading causes of mortality and morbidity worldwide. Estimated annual incidence of stroke in Pakistan is 250/100,000 translating to 350,000 new cases per year. The prognosis of patient depends mainly on the severity of the stroke. In this study we evaluated serum calcium as a marker of severity of ischemic stroke.

**Method:** This cross-sectional study was conducted at the Department of Medicine, Holy Family Hospital, Rawalpindi, Pakistan, on 132 patients who presented within 72 hours of acute ischaemic stroke, from April 1 to June 30, 2017. The diagnosis of acute ischaemic stroke was based on symptoms of focal neurologic deficit and computed tomography (CT) brain evidence of ischaemic infarct. Severity of stroke was assessed using NIHSS. Patients' serum calcium, albumin and renal function tests were obtained and the values along with patients' name, age, gender and residential address were recorded in the study pro forma. SPSS version 22 was used for data analysis. Pearson's correlation coefficient was calculated to investigate the bivariate relationship between serum calcium and stroke severity on NIHSS.

**Results:** Serum calcium of all 132 patients was measured and adjusted for serum albumin level. The mean serum calcium was  $8.74 \pm 0.58$  mg/dl (range: 7.24-10.81 mg/dl). The level of calcium was below 8.7 mg/dl in 40(34.06%) patients, 8.71-9.00 mg/dl in 35(23.19%), 9.01-9.30 mg/dl in 25(22.46%) and above 9.30 mg/dl in 32(20.3%) patients. The mean NIHSS of the respective groups was 21.56, 15.63, 18.56 and 16.25 respectively. Bivariate correlation was calculated between continuous data of serum

calcium and NIHSS. The overall Pearson's correlation coefficient was  $r = -0.318$ .

**Conclusion:** Lower serum calcium levels are associated with greater severity of ischaemic stroke as determined via NIHSS score.

**Key Words:** National institute health stroke score (NIHSS), Ischaemic stroke, Albumin corrected serum calcium level

## Introduction

WHO defines stroke as "a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 h or leading to death, with no apparent causes other than of vascular origin."<sup>1</sup> Stroke is one of the leading causes of mortality and morbidity worldwide. Its incidence is expected to double in coming years in our part of the world.<sup>2</sup> Risk factors include hypertension, diabetes mellitus, dyslipidaemia, smoking, family history of stroke and past episode of transient ischemic attack (TIA) or stroke. Pakistan is undergoing major economic and demographic changes in the recent years resulting in a paradigm shift from poverty-related infectious and nutritional deficiency diseases toward lifestyle-related cardiovascular and cerebrovascular diseases. So there is a need for reliable prognostic markers in order to assess the severity of stroke considering the economic burden it poses due to the disability associated with stroke. Exact data about the incidence and prevalence of stroke in Pakistan is lacking, but there is high prevalence of major risk factors for stroke in our population<sup>3</sup>, so the burden is assumed to be high.

Calcium (Ca) plays a pivotal role in the pathogenesis of ischemic stroke.<sup>4</sup> Cerebral ischemia causes intracellular accumulation of calcium resulting in a

cascade which eventually activates cytotoxic enzyme leading to cell death.<sup>5</sup> It has also been reported that high dietary intake of Calcium has been associated with reduced risk of stroke.<sup>6</sup>

Chung et al reported that higher albumin corrected serum calcium levels were associated with a poorer short-term outcome and greater risk of long-term mortality after acute ischemic stroke.<sup>7</sup> However, Ovabiagele et al reported a negative correlation between serum calcium and severity of ischemic stroke.<sup>8</sup> This was in concordance with the findings of a local study conducted recently by Ishfaq et al.<sup>9</sup> Moreover, another study done in Canada revealed that higher serum calcium levels was associated with smaller cerebral infarct volume.<sup>5</sup> Considering these contradictory findings we felt prompted to conduct this study evaluating the correlation between serum calcium level and severity of acute ischemic stroke. The results of this study will further add to the evidence regarding the role of calcium as a prognostic marker in acute ischemic stroke. It will further guide us to find out whether modifying dietary calcium in people at risk for stroke helps protect them against increased severity and reduced incidence of stroke.

## **Methods And Materials**

This cross-sectional study was conducted at the Department of Medicine, Holy Family Hospital, Rawalpindi, Pakistan, from January 1 to June 30, 2017. Sample size was calculated using correlation coefficient of  $r = -0.237^9$ , 95% power of test and 5% significance level, and non-probability consecutive sampling technique was used. The study was carried out after the approval from the institutional research forum. Both male and female patients aged above 18 years presenting within 72 hours of acute ischaemic stroke were included. Patients with chronic renal failure, malignancy and history of recurrent stroke were excluded. Patients with aspiration pneumonia on chest X ray (CXR) film and deranged renal functions were also excluded. The diagnosis of acute ischaemic stroke was based on symptoms of focal neurologic deficit and computed tomography (CT) brain evidence of ischaemic infarct. The purpose and benefits of the

study were explained to the patients and written informed consent was obtained.

All patients were subjected to detailed history and examination. Severity of stroke was assessed using NIHSS. A sample of 5cc of blood was taken from all patients without applying tourniquet under strict aseptic technique, and was sent to the hospital's laboratory on the same day and within 78 hours of onset of symptoms to measure serum calcium, albumin and renal function tests. Patients also underwent baseline investigations including CXR.

All the above-mentioned information including patients' name, age, gender and residential address was recorded in the study proforma. SPSS version 22 was used for data analysis. Mean and standard deviation (SD) was calculated for continuous variables like NIHSS and serum calcium. Categorical variables like gender were expressed as frequencies and percentages. Pearson's correlation coefficient was calculated to investigate the bivariate relationship between serum calcium and stroke severity on NIHSS.

## **Results**

Mean age of the study population ( $N = 132$ ) was  $57.98 \pm 8.3$  years (range 40-75). Mean age of male patients ( $n = 60$ ) was  $60.9 \pm 11.5$  years (range 45-75) and that of female patients ( $n = 72$ ) was  $55.78 \pm 7.3$  years (range 40-70).

The mean serum calcium was  $8.74 \pm 0.58$  mg/dl (range: 7.24-10.81 mg/dl). The level of calcium was below 8.7 mg/dl in 40(34.06%) patients, 8.71-9.00 mg/dl in 35(23.19%), 9.01-9.30 mg/dl in 25(22.46%) and above 9.30 mg/dl in 32(20.3%) patients. (Table I)

The overall mean NIHSS was  $18.24 \pm 5.86$  (range: 7-38). The risk factors most commonly detected were a past history of hypertension, previous stroke or TIA, smoking, high cholesterol and diabetes mellitus. Serum calcium of all patients was measured and adjusted for serum albumin level.(Table II)

The mean NIHSS of the respective groups was 21.56, 15.63, 18.56 and 16.25 respectively. Bivariate correlation was calculated between continuous data of serum calcium and NIHSS. The overall Pearson's correlation coefficient was  $r = -0.318$ . (Fig I)

Table I: Level of Calcium and mean NIHSS distribution

Level of Calcium(mg/dl)	Mean NIHSS*	N
< 8.71	21.56	40
8.71 - 9.00	15.63	35
9.01 - 9.30	18.56	25
> 9.30	16.25	32
Total	18.24	132

\* NIHSS: National institute of health stroke score

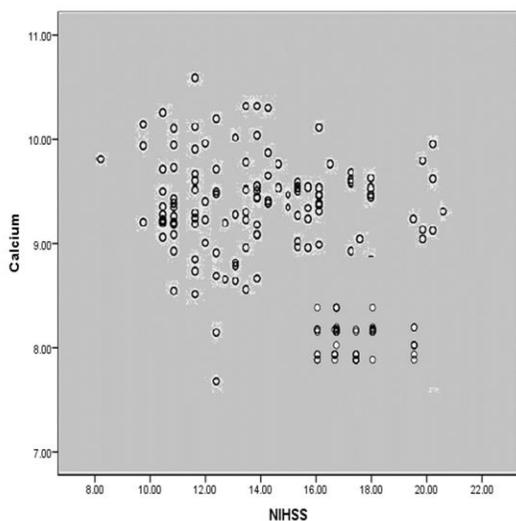


Figure I: Scatter plot of Serum Calcium vs NIHSS (N=132)

Table II: Frequency of risk factors of stroke

Risk Factors	Frequency	Percentage (%)
Hypertension	72	54.5
Previous stroke / TIA	36	27.3
Smoking	52	39.4
Diabetes	66	50.0
High Cholesterol	50	37.9

### Discussion

Stroke is a leading cause of long-term disability and the leading preventable cause of disability worldwide. Estimated annual incidence of stroke in Pakistan is 250/100,000 translating to 350,000 new cases per year.<sup>3</sup> Ischemic stroke occurs when blood flow to a certain part of brain drops below critical level leading to hypoxic insult. The resulting cellular hypoxia leads to calcium influx into the cells. Serum calcium levels

have a significant role in the molecular pathways of ischemic neuronal death and damage. The prognosis of patient depends mainly on the severity of the stroke. Various methods can be used to assess the severity e.g. infarct volume on CT, clinical assessment of severity and certain biochemical parameters like C reactive protein etc. In this study we embarked upon to assess serum calcium as a marker of severity of ischemic stroke.

The mean age of our study population was 57.98 years close to 61.09 years as reported by Ishfaq et al in a recent local study<sup>9</sup>. Guven H. et al. reported a mean age of 67 years.<sup>10</sup> Appel SA et al. reported a mean age of 70.7 years.<sup>11</sup> The difference was probably due to the fact that primary stroke prevention guidelines are not strictly followed and the average life expectancy is lower than developed nations as noted by Ishfaq et al<sup>9</sup>. The female to male ratio was 1.20:1 demonstrating a female preponderance in line with the findings of Ishfaq et al<sup>9</sup> and Guyen H et al.<sup>10</sup>

The mean serum calcium was 8.74±0.58 mg/dl in our cohort which was quite similar to that of Ishfaq et al<sup>9</sup>; however, it was considerably lower as compared to 9.2±0.5 mg/dl as reported by Appel SA et al.<sup>11</sup> Nutritional deficiency due to poor socioeconomic status of our population could be a potential reason.

Our study revealed a negative correlation between albumin adjusted serum calcium and severity of stroke as assessed by NIHSS ( $r = -0.318, p < 0.05$ ). Ishfaq et al and Guyen H et al also reported the same negative correlation between albumin adjusted serum calcium and NIHSS.<sup>8, 10</sup> In our study serum calcium level was measured within 48 to 72 hours of stroke as most of the people came from far flung areas with considerable delay before presenting to ER since the onset of initial symptoms. This proved useful to our study because the calcium levels that we measured were similar to the "delayed calcium" group of Ovbiagele *et al* which they found to correlate with lesser severity of stroke and better recovery at 3 months.<sup>8</sup> However albumin adjusted serum calcium did not correlated accordingly with stroke severity; rather, it was total calcium which correlated with severity of stroke as reported previously by Erasmo et al.<sup>12</sup>

The pathophysiological basis for the observed trend probably involves calcium influx via N-methyl-D-aspartate (NMDA) receptors.<sup>13</sup> Low Vitamin D levels offer another possible explanation for the increased severity of stroke seen in setting of low serum calcium levels.<sup>14</sup>

Though our study revealed an association between serum calcium level and severity of stroke but there were certain limitations as well. 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 severity of stroke, this study adds to the evidence and proves calcium levels to be a useful prognostic marker in stroke.

### **Conclusion**

Serum calcium levels may reflect the severity of ischaemic injury. Lower serum calcium levels are associated with greater severity of ischaemic stroke as determined via NIHSS score.

### **Acknowledgements**

We are highly thankful to Dr. Faiza Aslam for guiding us throughout our research project.

### **References**

1. World Health Organization. Preventing Chronic Diseases-A Vital Investment: WHO Global Report. World Health Organization; 2005.
2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *The Lancet Neurology* 2009 30; 8(4):355-69.
3. Khealani BA, Hameed B, Mapari UU. Stroke in Pakistan. *J Pak Med Assoc* 2008; 58:400-3.
4. Bano D, Nicotera P. Ca<sup>2+</sup> Signals and neuronal death in brain ischemia. *Stroke* 2007; 38: 674-6.
5. 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.
6. Umesawa M, Iso H, Ishihara J, Saito I, Kokubo Y, Inoue M, et al. Dietary calcium intake and risks of stroke, Its Subtypes, and Coronary Heart Disease in Japanese: The JPHC Study Cohort I. *Stroke* 2008; 39:2449-56.
7. Chung JW, Ryu WS, Kim BJ, Yoon BW. Elevated calcium after acute ischemic stroke: association with a poor short-term outcome and long-term mortality. *Journal of stroke* 2015 Jan; 17(1):54.
8. Ovbiagele B, Starkman S, Teal P, Lyden P, Kaste M, Davis SM, Hacke W, Fierus M, Saver JL. Serum calcium as prognosticator in ischemic stroke. *Stroke* 2008 Aug 1; 39(8):2231-6.
9. Ishfaq M, Ullah F, Akbar S, Rahim F, Afridi AK. Correlation of serum calcium with severity of acute ischaemic stroke. *JPM. The Journal of the Pakistan Medical Association* 2017 Jan; 67(1):20-3.
10. Guven H, Cilliler 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.
11. Appel SA, Molshatzki N, Schwammenthal Y, Merzeliak 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.
12. D'Erasmus E, Pisani D, Romagnoli S, Ragno A, Acca M. Acute serum calcium changes in transient ischemic attack and cerebral infarction. *Journal of medicine* 1998; 29(5-6):33-7.
13. MacDonald JF, Xiong ZG, Jackson MF. Paradox of Ca<sup>2+</sup> signaling, cell death and stroke. *Trends Neuro Sci* 2006; 29:75-81.
14. Marniemi J, Alanen E, Impivaara O, Seppanen R, Hakala P, Rajala T, et al. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr Metab Cardiovasc Dis* 2005; 15:188-97.