

## Correlation of serum calcium with severity of acute ischaemic stroke

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### Abstract

**Objective:** To determine the correlation of serum calcium with severity of acute ischaemic stroke.

**Methods:** This cross-sectional study was conducted at the Khyber Teaching Hospital, Peshawar, Pakistan, from January to September 2013, and comprised patients who had suffered ischaemic stroke. All patients aged above 18 years who had been diagnosed to have suffered ischaemic stroke through history, physical examination and computed tomography scan, and who were admitted within the first 72 hours of the onset of the illness were included. Serum calcium was obtained within 78 hours of the onset of stroke and the severity of stroke was assessed at the same time using the National Institute of Health Stroke score.

**Results:** Of the 138 patients, 71 (51.4%) were women and 67 (48.6%) men. The overall mean age was 61.09±11.93 years (range: 34-100 years). The mean National Institute of Health Stroke score was 17.77±7.73 (range: 2-35). Serum calcium of all patients was measured and adjusted for serum albumin level. The mean serum calcium level was 8.82±0.69 mg/dl (range: 6.84-10.48). Bivariate correlation was calculated for continuous data of serum calcium and National Institute of Health Stroke score. The overall Pearson's correlation coefficient was  $r = -0.237$  ( $p = 0.005$ ).

**Conclusion:** Lower serum calcium levels may be associated with more severe clinical findings at the onset of stroke.

**Keywords:** Ischaemic stroke, Stroke severity, NIHSS score, Serum calcium. (JPMA 67: 20; 2017)

### Introduction

Stroke is the second-largest cause of mortality worldwide and the third-largest in the industrialised world.<sup>1</sup> According to World Health Organisation's (WHO) estimates, 16.3 million new stroke events occur each year across the world.<sup>2</sup> It is the most common cause of adult disability in the United States (US).<sup>3</sup> The incidence of stroke is increasing in Asia and is responsible for significant economic burden and is having a devastating impact on patients, their families and health care system.<sup>4</sup> Exact data about the incidence and prevalence of stroke in Pakistan is lacking, but the burden is assumed to be high because of the high prevalence of major risk factors for stroke in our population.<sup>5</sup>

Stroke is defined as a syndrome of rapid onset of cerebral deficit, usually focal, lasting more than 24 hours or leading to death with no cause apparent other than the vascular one.<sup>6</sup> The burden of ischaemic stroke is increasing worldwide because of the rise in the major risk factor for ischaemic stroke i.e. hypertension, diabetes, obesity, smoking and dyslipidaemia.<sup>6,7</sup> Certain novel risk factors such as factor V Leiden, leucocyte count, high-sensitivity C-reactive protein (CRP), interleukins (IL-6, IL-18),

cytomegalovirus (CMV), herpes simplex virus, fibrinogen, platelet aggregation, homocysteine, metabolic syndrome, insulin resistance, B-type natriuretic peptide (BNP), microalbuminuria, cystatin C and serum calcium are increasingly being found to be associated with risk and severity of ischaemic stroke.<sup>8,9</sup> Calcium plays an important role in the pathogenesis of ischaemic stroke.<sup>9</sup> Cerebral ischaemia results in intracellular accumulation of calcium which activates cytotoxic enzyme leading to cell death.<sup>10</sup> A study conducted in the US has shown that low serum calcium found after acute ischaemic stroke is significantly associated with greater severity of stroke as assessed by the National Institute of Health Stroke Score (NIHSS) with a correlation coefficient of  $r = -0.3$  than those with high calcium levels.<sup>11</sup> A study done in Canada has revealed that higher serum calcium levels are associated with smaller cerebral infarct volume ( $r = -0.199$ ).<sup>10</sup> Another US study has shown that high serum calcium at the time of hospital admission is associated with less severe stroke and improved functional outcome at discharge.<sup>12</sup> A study conducted in Japan showed that dietary calcium intake, especially calcium from dairy products, was found to be associated with a reduced incidence of stroke.<sup>13</sup>

The current study was planned to determine whether serum calcium levels at presentation are correlated with the severity of acute ischaemic stroke in our population. The results of this study will be projected to various healthcare institutions and guidelines will be suggested regarding early correction of serum calcium in case of

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finding negative correlation in our study. Thus, patients with severe stroke can be referred and managed in specialised units. This study will also guide us to further research work to find out whether modifying dietary calcium in people at risk for stroke helps protect them against increased severity and reduced incidence of stroke.

## Patients and Methods

This cross-sectional study was conducted at the Department of Medicine, Khyber Teaching Hospital, Peshawar, Pakistan, from January 1 to September 30, 2013. Sample size was calculated using correlation coefficient of  $r = -0.3$ , 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 ethical committee. 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 above-mentioned conditions acted as confounders and, if included, would have introduced bias in the study results. 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 test. Patients also underwent baseline investigations including CXR. Serum calcium level was measured under the supervision of a pathologist with more than 10 years of experience in chemical pathology.

All the above-mentioned information including patients' name, age, gender and residential address was recorded in the study pro forma. SPSS 16 was used for data analysis. Mean and standard deviation (SD) were 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

Of the 138 patients, 71(51.4%) were women and 67(48.6%) were men, with a female-to-male ratio of 1.06:1. Their mean age was  $61.09 \pm 11.93$  years (range: 34-100 years). The mean age of women was  $60.69 \pm 12.34$  years

**Table:** Level of calcium and mean NIHSS distribution (N=138).

Level of calcium	Mean NIHSS	N	Std. Deviation
Less than 8.7 mg/dl	20.19	47	7.865
8.71-9.00 mg/dl	14.81	32	7.324
9.01-9.30 mg/dl	19.81	31	6.199
More than 9.30 mg/dl	14.82	28	7.727
Total	17.77	138	7.737

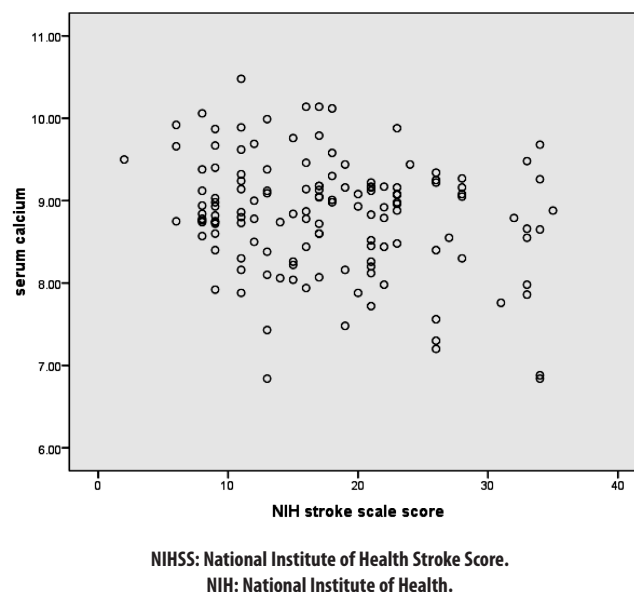
Std.: Standard

NIHSS: National Institute of Health Stroke Score.

(range: 34-92 years) while that of men was  $61.52 \pm 11.55$  years (range: 40-100 years). Moreover, 103(74.64%) of all the patients fell in the age group of 46-75 years.

The overall mean NIHSS -was  $17.77 \pm 7.73$  (range: 2-35).

Serum calcium of all patients was measured and adjusted for serum albumin level. The mean serum calcium -was  $8.82 \pm 0.69$  mg/dl (range: 6.84-10.48 mg/dl). The level of calcium was below 8.7 mg/dl in 47(34.06%) patients, 8.71-9.00 mg/dl in 32(23.19%), 9.01-9.30 mg/dl in 31(22.46%) and above 9.30 mg/dl in 28(20.3%) patients. The mean NIHSS of the respective groups was  $20.19 \pm 7.865$ ,  $14.81 \pm 7.324$ ,  $19.81 \pm 6.199$  and  $14.82 \pm 7.727$  (Table).



**Figure:** NIHSS versus serum calcium scatter plot (N=138).

Bivariate correlation was calculated between continuous data of serum calcium and NIHSS. The overall Pearson's correlation coefficient was  $r = -0.237$  ( $p = 0.005$ ). The value was  $r = -0.256$  ( $p = 0.37$ ) among men and  $r = -0.193$  among women ( $p = 0.10$ ) (Figure).

## Discussion

Stroke is one of the leading causes of mortality and morbidity in the world.<sup>1</sup> Stroke has multiple risk factors like hypertension, hyperlipidaemia, diabetes, smoking, atrial fibrillation, valvular heart diseases and vasculitis.<sup>6</sup> The severity of ischaemic stroke can be assessed by clinical examination, imaging to quantify infarct volume and certain biochemical markers. Studies have been done to correlate the severity of stroke with these biochemical markers to know their importance from prognostic point of view.

A female-to-male ratio of 1.06:1 in the current study was in accordance with an international study conducted by Guven H. et al., who have shown a male-to-female ratio of 1:1.13.<sup>14</sup> Buck BH et al. have also shown a female preponderance in their study with a male-to-female ratio of 1: 1.40.<sup>10</sup> But Appel SA et al. have shown a male preponderance with a male-to-female ratio of 1.35:1.<sup>15</sup> There were no local studies available on this topic so we could not compare our results with local studies.

Most of our patients (74.64%) were in the age group of 46-75 years. This is again in accordance with data already available. The mean age of our patients was  $61.09 \pm 11.933$  years. Guven H. et al. reported a mean age of 67 years.<sup>14</sup> Appel SA et al. reported a mean age of 70.7 years.<sup>15</sup> A low mean age in our study was in accordance with the fact that primary stroke prevention guidelines are not strictly followed and risk factors like hypertension, diabetes, etc. are not controlled in our country due to poverty. The average life expectancy is also lower in our country as compared to developed nations.

The mean serum calcium in our study was  $8.82 \pm 0.69$  mg/dl as compared to mean albumin adjusted calcium of  $9.2 \pm 0.5$  mg/dl in another study.<sup>15</sup> The lower mean calcium in our study can be due to many reasons. First, our patients were from lower to middle socio-economic class and lower calcium compared to international studies could be due to poor nutritional status. Second, the lower calcium level could be due to poor sunlight exposure, especially in women among whom the mean calcium in our study was  $8.71 \pm 0.68$  mg/dl because most of our women remain inside their homes and wear veils. Patients in our study with lower calcium levels were mostly females which is comparable to the finding of other studies.<sup>14,15</sup>

In our study the mean age of the patients was higher in the group with low serum calcium. Guven H. et al. have reported the same findings in their study.<sup>16,17</sup> Ovbiagele B. et al. have also reported that patients with low mean age had high serum calcium.<sup>11</sup>

The mean NIHSS in our study within 48 to 72 hours of onset of symptoms was higher in lower calcium groups than other groups. This is in accordance with other studies.<sup>10,11,14</sup>

There are very few studies which look at the correlation of serum calcium with severity of stroke and its prognostic significance in acute ischaemic stroke. The level of calcium is found to be low in transient ischaemic attack and more substantial fall occurs in ischaemic cerebral infarction than TIA.<sup>16</sup> Our study revealed a negative correlation between serum calcium and severity of stroke as assessed by NIHSS ( $r = -0.237$ ,  $p < 0.05$ ). Lower albumin adjusted calcium values measured within 48 to 72 hours of ischaemic stroke are associated with more severe clinical findings. Guven H. et al. have reported the same negative correlation but it was different from our study as the serum calcium was measured in first 24 hours.<sup>14</sup> Ovbiagele et al. evaluated the impact of calcium and magnesium on stroke severity. They found that higher serum calcium was significantly associated with lesser severity of stroke and better discharge functional outcome.<sup>17</sup> In another study conducted by Ovbiagele B et al., both early ( $< 4.5$  hours) and late (72 to 96 hours) calcium was correlated with stroke severity. The results of that study showed that early serum calcium levels correlated poorly with baseline NIHSS ( $r = -0.05$ ,  $p = 0.21$ ), and 72 to 96 hours NIHSS ( $r = -0.10$ ,  $p = 0.01$ ) and thus had no prognostic significance.<sup>11</sup> But elevated calcium obtained at 72 to 96 hours of ischaemic stroke showed a stronger correlation with baseline NIHSS ( $r = -0.2$ ,  $p = 0.0001$ ) and 72 to 96 hours NIHSS ( $r = -0.3$ ,  $p < 0.0001$ ); it was associated with lesser severity of stroke and better 3-month functional outcome.<sup>11</sup> In our study we obtained serum calcium within 48 to 72 hours of onset of stroke and it reflects delayed calcium. Secondly, most of our patients presented late as they came from far-flung areas. Health facilities are underdeveloped in rural areas and peripheral districts. A study found that higher total serum calcium on admission is associated with smaller cerebral infarct volume on magnetic resonance imaging (MRI).<sup>10</sup>

Several explanations have been given for the association of relatively low calcium with stroke severity and poor outcome. Low calcium may be due to tissue ischaemia in which there is intracellular calcium accumulation. In neuronal cell death due to ischaemia, many mechanisms

account for this such as excitatory pathway, oxidative stress, apoptosis and necrotic cell death.<sup>18</sup> Recent studies have suggested that calcium influx via N-methyl-D-aspartate (NMDA) receptor triggers these events.<sup>18,19</sup> High dietary calcium intake has been associated with reduced incidence of stroke.<sup>13</sup> Another explanation is that low calcium reflects low levels of vitamin D which itself is directly associated with poor outcome.<sup>20</sup> Low vitamin D is also associated with increased risk of stroke.<sup>21</sup> If low calcium potentiated ischaemic injury, it would be predicted that raising the calcium might have neuroprotective effect. Proper studies need to be done to evaluate this effect.

This study revealed an association between serum calcium level and severity of stroke but there were certain limitations as well. There were no local studies available on the topic for comparison.

### Conclusion

Lower serum calcium levels may be associated with more severe clinical findings at the onset of stroke. Serum calcium levels may reflect the severity of ischaemic injury. Prospective trials will be required to clarify the mechanism of this effect and to assess the role of serum calcium level as a prognostic variable and of calcium modulation as part of a strategy for prevention of stroke.

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