IMPORTANCE Calcium is a key cofactor of the coagulation cascade and may play a role in the pathophysiology of intracerebral hemorrhage (ICH).

OBJECTIVE To investigate whether a low serum calcium level is associated with an increase in the extent of bleeding in patients with ICH as measured by baseline hematoma volume and risk of hematoma expansion.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of 2103 consecutive patients with primary ICH ascertained during the period between 1994 and 2015 at an academic medical center. The statistical analysis was performed in January 2016.

MAIN OUTCOMES AND MEASURES Total calcium level was measured on admission, and hypocalcemia was defined as a serum calcium level of less than 8.4 mg/dL. Baseline and follow-up hematoma volumes, detected by noncontrast computed tomography, were measured using a computer-assisted semiautomated analysis. Hematoma expansion was defined as an increase of more than 30% or 6 mL from baseline ICH volume. Associations between serum calcium level and baseline hematoma volume and between serum calcium level and ICH expansion were investigated in multivariable linear and logistic regression models, respectively.

RESULTS A total of 2123 patients with primary ICH were screened, and 2103 patients met the inclusion criteria (mean [SD] age, 72.7 [12.5] years; 54.3% male patients), of whom 229 (10.9%) had hypocalcemia on admission. Hypocalcemic patients had a higher median baseline hematoma volume than did normocalcemic patients (37 mL [IQR, 15-72 mL] vs 16 mL [IQR, 6-44 mL]; P < .001). Low calcium levels were independently associated with higher baseline ICH volume (β = -0.13, SE = .03, P < .001). A total of 1393 patients underwent follow-up noncontrast computed tomography and were included in the ICH expansion analysis. In this subgroup, a higher serum calcium level was associated with reduced risk of ICH expansion (odds ratio, 0.55 [95% CI, 0.35-0.86]; P = .01), after adjusting for other confounders.

CONCLUSIONS AND RELEVANCE Hypocalcemia correlates with the extent of bleeding in patients with ICH. A low calcium level may be associated with a subtle coagulopathy predisposing to increased bleeding and might therefore be a promising therapeutic target for acute ICH treatment trials.
Serum Calcium Level and Extent of Bleeding in Intracerebral Hemorrhage

**Key Points**

**Question** Does serum calcium play a role in the pathophysiology of intracerebral hemorrhage (ICH)?

**Findings** In this cohort study of 2103 patients, hypocalcemia was associated with larger baseline ICH volume (37 mL in hypocalcemic patients vs 16 mL in normocalcemic patients). In a subset of patients, higher serum calcium level on admission was significantly associated with a reduced risk of ICH expansion.

**Meaning** A low serum calcium level is associated with an increase in the extent of bleeding in patients with ICH and may be a promising therapeutic target.

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Spontaneous intracerebral hemorrhage (ICH) is one of the most catastrophic types of stroke, associated with high mortality and morbidity. Both baseline hematoma volume and hematoma expansion are predictors of outcome in patients with ICH. It has been suggested that a lower serum calcium level is associated with higher hematoma volume in patients with ICH, as well as hemorrhagic transformation after intravenous thrombolysis for acute ischemic stroke. However, systematic studies on the topic are currently lacking, and the underlying mechanisms are poorly understood. One possibility is that serum calcium is involved in platelet function and in several steps of the coagulation cascade. Therefore, patients with a low calcium level may have impaired hemostasis. Another possibility is that serum calcium may induce arterial relaxation and secondary blood pressure (BP) reduction through activation of perivascular receptors. Low levels of calcium may therefore lead to hematoma enlargement through elevated BP.

To examine whether serum calcium levels play a role in the pathophysiology of ICH, we performed an analysis in a large cohort of patients with acute ICH. First, we explored the association between a low calcium level and larger ICH volume, and we investigated whether this association is mediated by impaired coagulation or hypertension. Second, we examined whether low calcium levels are associated with an increased risk of hematoma expansion.

**Methods**

**Study Design and Patient Selection**

All aspects of the study were approved by the institutional review board of Massachusetts General Hospital. Written or oral informed consent was obtained by patients or family members or was waived by the institutional review board.

We performed a retrospective analysis of an ongoing prospective cohort of patients with spontaneous ICH at a single academic hospital from January 1994 to April 2015. The inclusion criteria were (1) a diagnosis of spontaneous ICH that was detected by noncontrast computed tomography (NCCT) performed within 72 hours from the presumed symptom onset; and (2) a total serum calcium measurement obtained on admission. Participants were excluded if there was evidence of (1) traumatic intracranial hemorrhage, (2) intracranial tumor or vascular malformations presumed to be the cause of the hemorrhage, (3) primary intraventricular hemorrhage, or (4) hemorrhagic conversion of acute ischemic stroke.

Hypocalcemia on admission was defined as a total serum calcium level of less than 8.4 mg/dL (to convert to millimoles per liter, multiply by 0.25). Both total calcium and albumin-corrected calcium measurements can underestimate the presence of hypocalcemia. Therefore, we repeated our analysis in a subgroup of patients, using ionized rather than total calcium because ionized calcium more accurately reflects the physiologically active component of serum calcium.

**Image Acquisition and Analysis**

All images were analyzed by study staff members blinded to all clinical and laboratory variables. The NCCT scans were acquired with an axial technique and 5-mm-thick slices, 120 to 140 kilovolts (peak) [kV(p)], 10 to 500 mA, and reviewed for determination of ICH location. Our institutional protocol recommended routinely performing NCCT of the head at 24-hour intervals or in cases of neurological deterioration.

Baseline and follow-up hematoma volumes detected on NCCT scans were calculated using AnalyzeDirect 11.0 software, a semiautomated computer-assisted technique. The ICH expansion analysis was performed in the subgroup with a follow-up NCCT scan available. Hematoma expansion was defined as an increase of more than 30% or 6 mL from baseline ICH volume.

Computed tomography angiography (CTA) image acquisition was performed by scanning from the base of the skull to the vertex using an axial technique, 0.5 pitch, 1.25-mm collimation, 100 to 140 kV(p), with a tube current ranging from 100 to 630 mA. Iodinated contrast material (65-85 mL) was administered by a power injector at 4 to 5 mL/s into an antecubital vein with SmartPrep (GE Medical Systems), a semiautomatic contrast bolus triggering technique. The CTA images were reviewed for the presence of a spot sign as previously described.

**Clinical Variables**

Demographic and clinical data were systematically collected through interviews with patients and family members and through a retrospective review of hospital medical records. We assessed the presence of a medical history of hypertension, diabetes, hypercholesterolemia, antiplatelet therapy, oral anticoagulant treatment (OAT); systolic and diastolic blood pressure on admission; and time from symptom onset to baseline NCCT, as previously described in detail. Elevated BP was managed according to the American Heart Association/American Stroke Association Guidelines.

**Statistical Analysis**

Categorical variables were expressed as counts (%), whereas continuous variables were expressed as mean (SD) or median (interquartile range [IQR]) values. The differences between patients with and patients without hypocalcemia on admission were examined using the χ² test, the t test, or the Mann-Whitney U test as appropriate. The correlation between continuous variables was assessed with the Spearman test.
Multivariable linear regression was used to analyze the association between calcium level and baseline hematoma volume. The ICH volume, calcium level, and time from onset to NCCT were log-transformed to approximate the normal distribution. Age, sex, time from onset to NCCT, and all variables with \( P < .10 \) in the univariable analysis were included in the multivariable linear regression model. Because impaired hemostasis is one of the possible mechanisms underlying the association between serum calcium level and extent of bleeding, OAT-associated cases and non–OAT-associated cases were analyzed separately in all linear regression analyses. The association between calcium level and ICH expansion was examined in a multivariable logistic regression analysis, adjusted for known predictors of hematoma expansion.19,20 An individual patient’s predicted probability of ICH expansion was derived from individual data and from the binary logistic regression model estimates and was expressed as a continuous variable ranging from 0 to 1. \( P < .05 \) was considered to be statistically significant. All analyses were performed using the statistical package SPSS version 21 (http://www.spss.com).

Results

A total of 2123 patients with primary ICH were screened, and 2103 patients met the inclusion criteria (mean [SD] age, 72.7 [12.5] years; 54.3% male patients), of whom 229 (10.9%) had hypocalcemia on admission. The median baseline ICH volume was 18 mL (IQR, 6–48 mL), and the median time from symptom onset to baseline NCCT was 4 hours (IQR, 2–8 hours). Figure 1 summarizes the cohort selection process, and the characteristics of the study population are shown in the eTable in the Supplement.

The clinical, demographic, and imaging characteristics were similar between the study participants and the excluded patients (all \( P > .10 \)). Table 1 shows that hypocalcemic patients had a higher median baseline hematoma volume than did the normocalcemic patients (37 mL [IQR, 15–72 mL] vs 16 mL [IQR, 6–44 mL]; \( P < .001 \)). Patients with hypocalcemia on admission were also younger than those without (mean [SD] age, 68.9 [13.1] years vs 73.1 [12.4] years; \( P < .001 \)) and less frequently received antithrombotic medications (42.8% vs 49.7%; \( P = .049 \)). The mortality rate at 30 days was significantly higher among hypocalcemic patients than normocalcemic patients (59.8% vs 44.2%; \( P < .001 \)).

Ionized calcium levels on admission were available for a subgroup of patients (526 of 2103 [25.0%]) and correlated well with total serum calcium levels (\( \rho = 0.217, P < .001 \)). The ionized calcium level was inversely correlated with the international normalized ratio on admission (\( \rho = -0.206, P < .001 \)) and the activated partial thromboplastin time (\( \rho = -0.112, P = .02 \)). Conversely, there was no significant association between calcium level and BP on admission (\( \rho = 0.061, P = .18 \) for systolic BP; \( \rho = 0.057, P = .21 \) for diastolic BP).
Baseline Hematoma Volume Analysis

Analyzing total calcium levels on admission for all ICH cases, we found that the multivariable linear regression model (Table 2) showed a significant association between serum calcium level and baseline hematoma volume ($\beta = -0.13$, SE = 0.03, $P < .001$). Performing the multivariate linear regression analysis stratified by OAT, we found that the association between serum calcium level and ICH volume was stronger for non–OAT-associated cases ($\beta = -0.14$, SE = 0.03, $P < .001$) than OAT-associated cases ($\beta = -0.12$, SE = 0.06, $P = .04$).

When ionized calcium level on admission was analyzed, we confirmed a significant inverse association between calcium level and baseline hematoma volume ($\beta = -0.20$, SE = 0.07, $P = .004$). This association remained statistically significant in non–OAT-associated cases ($\beta = -0.19$, SE = 0.08, $P = .02$) but not in OAT-associated cases ($\beta = -0.18$, SE = 0.15, $P = .21$), as shown in Table 2.

Hematoma Expansion Analysis

A total of 1393 patients (66.2%) had a follow-up NCCT scan available and were included in the ICH expansion analysis. A higher serum calcium level on admission was significantly associated with a reduced risk of ICH expansion in multivariable logistic regression (odds ratio, 0.72 [95% CI, 0.54-0.97]; $P = .03$). This association also remained significant when the presence of a CTA-detected spot sign was included in the multivariable logistic regression model (Table 3). We obtained the same results when ionized calcium was analyzed in the multivariable regression model (Table 3). The serum calcium level on admission was inversely correlated with baseline ICH volume and predicted the probability of hematoma expansion in a linear, dose-dependent relationship (Figure 2).

These results were unchanged when the serum calcium level was analyzed as a dichotomous variable in the multivariable linear and logistic regression models. The presence of hypocalcemia on admission was indeed associated with a larger initial ICH volume ($\beta = 0.15$, SE = 0.03, $P < .001$) and an increased risk of hematoma expansion (odds ratio, 4.81 [95% CI, 1.21-19.16]; $P = .03$). Finally, we confirmed the association between serum calcium level, baseline ICH volume ($\beta = -0.13$, SE = 0.04, $P = .002$), and risk of hematoma expansion (odds ratio, 0.42 [95% CI, 0.20-0.88]; $P = .02$) in the subgroup of patients who were receiving antiplatelet agents (n = 1029).

Discussion

Our findings corroborate and extend previous evidence of a relationship between lower levels of serum calcium and higher baseline ICH volume, and they provide further insights into the possible mechanisms for this association. In addition, we provide important novel data showing that a low serum calcium level is also associated with an increased risk of hematoma expansion.

Taken together, these findings raise the intriguing possibility that calcium plays a role in the pathophysiology of ICH. Two potential mechanisms are an effect of calcium on BP and an effect on coagulation status. 

First, calcium may play a role in vascular reactivity. Hypocalcemia could therefore lead to higher BP because of increased arterial vascular tone. However, in this cohort, we did not observe any significant association between calcium level and BP on admission. In addition, a history of hypertension was less common in patients with a lower serum calcium level on admission. Finally, any effect on hypertension might be expected to disproportionately affect deep rather than lobar ICH, but we did not observe an increased proportion of deep hematomas in hypocalcemic patients. Our results therefore do not support the hypothesis that a low serum calcium level influences the extent of bleeding through higher BP.

Conversely, our findings indirectly support the hypothesis that a low serum calcium level contributes to a larger ICH.
volume and an increased risk of hematoma expansion through impaired coagulation. In our study, the association between a low calcium level and a higher hematoma volume was stronger in non–OAT-associated ICH cases. This may reflect the fact that patients with OAT-associated ICH already have important alterations in coagulation physiology. Therefore, any effect of a low serum calcium level on the coagulation cascade may be less important in this category. Another potential explanation for this finding is the relatively small sample size of this subgroup, which prevented us from detecting an association as observed in non–OAT-associated cases. We also observed a significant inverse correlation between serum calcium level on admission, international normalized ratio, and activated partial thromboplastin time. Further evidence in favor of this hypothesis comes from the observation of a higher frequency (although not statistically significant) of CTA-detected spot signs in hypocalcemic patients. This imaging marker likely reflects active bleeding, is more commonly detected in patients with impaired hemostatic function, and is strongly associated with hematoma expansion.

From a clinical and therapeutic perspective, hematoma volume on admission and ICH expansion are potentially modifiable determinants of ICH outcome and, therefore, represent appealing targets for several ICH therapeutic strategies. Given the influence of serum calcium level on ICH volume and expansion, there may be a therapeutic opportunity. It may be that optimizing calcium homeostasis can play a role in preventing hematoma expansion once ICH occurs.

Some limitations of our study should be acknowledged. First, our results are based on a single-center, retrospective analysis. Second, participants were recruited over a long period of time, and therefore changes in ICH management during this period, especially regarding BP treatment, might have influenced our analysis. Third, we were not able to analyze pre-ICH calcium levels, and therefore we cannot exclude the possibility that hypocalcemia represents the consequence, rather than the cause, of significant blood extravasation. Fourth, the only markers of coagulation available routinely in this cohort were activated partial thromboplastin time and international normalized ratio. Advanced techniques such as thrombelastography may provide a better evaluation of coagulation activity. Our findings are therefore best interpreted as hypothesis generating, and further studies are needed to confirm that impairment of the coagulation system is the pathophysiological link connecting a low serum calcium level with an increase in the extent of bleeding. Finally, the ionized calcium level was not routinely measured and was therefore missing for a large proportion of patients.

Conclusions

We found an association between a low serum calcium level and the extent of bleeding in patients with ICH; impaired coagulation may be the biological mechanism underlying this association. Baseline hematoma volume and ICH expansion are potentially modifiable determinants of ICH outcome. Further large prospective studies are needed to confirm our findings and investigate whether serum calcium could be a therapeutic target for ICH clinical trials.
take responsibility for the integrity of the data and the accuracy of the data analysis.

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