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Study of association of serum vitamin D and serum calcium with spontaneous aneurysmal subarachnoid haemorrhage in a tertiary care centre

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Keywords
hypocalcaemia, hypovitaminosis, ASAH (aneurysmal subarachnoid haemorrhage), bleeding

ABSTRACT

Background: Aneurysmal subarachnoid haemorrhage (aSAH) is a disease associated with high mortality and morbidity. Recent studies have postulated a correlation between Vitamin D deficiency and aSAH, however, the mechanism of which remains obscure. Vitamin D and Calcium in patients withaSAH has not been formally investigated. Therefore, the aim of this study was to evaluate the incidence of hypovitaminosis D and hypocalcemia in patients with aSAH.

Methods: An observational study was conducted at the Department of Neurosurgery at tertiary care centre, New Delhi, India. 40 patients with spontaneous aneurysmal SAH were enrolled during the period January 2019 to 15th April 2020. The standard protocol of care was given to all patients included in the study. Laboratory investigations including Vitamin D and Calcium levels; Clinical examination and grading were done for each patient. The data thus collected was used to see the clinic-demographic profile of patients of aSAH with an emphasis on Vitamin D and Calcium levels.

Results: The study reported mean vitamin D level of 17.4 ± 7 ng/ml; mean calcium level of 8.3 ± 0.9 mg/dl amongst the study participants. Out of 40 patients, 8 patients (20%) were severely deficient, 24 patients (60%) were mild to moderate deficient and 8 patients (20%) were having normal vitamin D levels. 50% of the patients (n=20) were hypocalcaemic and 50% were normocalcaemic.

Conclusion: A higher incidence of vitamin D deficiency was observed in our study along with an equal incidence of hypocalcemia vs normocalcemia. Further studies with a comparison group and a bigger sample size are needed to validate this evidence.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is the extravasation of blood into subarachnoid space of the CNS, which is normally filled with

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cerebrospinal fluid (CSF). The prevalence of Subarachnoid Haemorrhage (SAH) is approximately 9 per 100,000 person per year[1]. There is a slight preponderance in women as compared to men, and this increases with age. Peak incidence has been observed in 5th and 6th decade of life[2]. The commonest cause of SAH overall is trauma, whereas commonest cause of spontaneous SAH is rupture of intracranial aneurysms[3]. About 80% of non-traumatic SAH happens due to aneurysms[4].

Most common symptom of SAH is headache, which is referred to by the patient as the worst headache he/she has ever experienced in his/her life. It can also be accompanied by nausea, vomiting, loss of consciousness.

Aneurysmal subarachnoid haemorrhage (aSAH) is a disease associated with a high mortality and morbidity. A study from Netherlands reported that the overall mortality rate of non-traumatic SAH has been found out to be 30%[5]. SAH because of the rupture of an intracranial aneurysm is a potentially fatal event .Altough it accounts for 5% of all strokes but its burden is relevant due to high mortality ,high disability and higher incidence in the young[6]. Even after good outcome of SAH, long term cognitive deficits (commonly in memory, language and executive functions) may happen to patients. Further, a study reported that approximately 40% of SAH survivors may not be able to return back to their previous jobs[7].Even after successful aneurysmal clipping in patients with aSAH, overall quality of life was found to be decreased as compared to controls in a study[8].

Recent studies have postulated a correlation between Vitamin D deficiency and aSAH, however the mechanism of which remains obscure[9,10,11]. Probable mechanisms that have been postulated are indirect variations in blood pressure[9], anti-proliferative and anti-inflammatory action of Vitamin D on smooth muscle of blood vessels[10]. These effects of vitamin D becomes more important as cerebral vasospasm has been implicated as a major causative factor for long term neurological deficits present in patients with SAH.

In the past decade, there has been a surge of interest in the impact of vitamin D levels on various conditions ranging from bony fractures to malignancy. A growing body of evidence also implicates hypovitaminosis D in cerebral small-vessel disease and stroke[12,13].Recent investigations, primarily in the cardiothoracic[14,15]and vascular surgeryliterature, have suggested a concordance of hypovitaminosis D and arterial disease, including aneurysmal dilation of the aorta[16].This relationship is believed to be mediated by a variety of mechanisms, including modulation of vessel wall inflammation, changes in vascular smooth muscle cell development, and numerous systemic effects such as changes in insulin resistance and lipid processing[17].

Hypocalcaemia has been significantly associated with extent of bleeding in patients with intracerebral haemorrhage because magnesium and calcium have roles in platelet function and coagulation cascade[18]. However, research regarding the association of intracranial aneurysm rupture risk in hypocalcaemia and hypomagnesemia are lacking. Vitamin D and Calcium in patients with cerebral aneurysms and aneurysmal SAH has not been formally investigated. Therefore, the aim of this study was to evaluate the incidence of hypovitaminosis D and hypocalcemia in patients with aSAH.

Methods

This was an observational study conducted at the Department of Neurosurgery at tertiary care centre New Delhi, India. 40 patients with spontaneous aneurysmal SAH were enrolled during the period January 2019 to 15th April 2020. All cases of spontaneous aneurysmal SAH admitted in the institute during the study period were included and patients who had a previous history of renal disease; history of liver dysfunction; history of chronic intestinal malabsorption; and those taking Vitamin D and Calcium supplementation for any reason were excluded from the study.

Informed written consent was taken from each eligible patient before his/her enrolment. The baseline evaluation included Personal and family history including any comorbidities or prior surgical intervention; General physical examination and thorough neurological evaluation; Laboratory tests including complete blood count (CBC), Liver function tests (LFTs), Renal function tests (RFTs); Non-contrast enhanced CT (NCCT) head; CT Angiography/ MR Angiography/DSA; Serum Calcium levels; and Vitamin D (25-hydroxyvitamin D) levels using radioimmunoassay method.

Standard protocol of care was given across to all patients included in the study. Grading was done by

the World Federation of Neurological Societies (WFNS) Grading of SAH, Modified Fisher grade, Hunt and Hess grade and Glasgow Coma Scale (GCS).

Mayo Medical laboratories reference ranges for Total serum 25-hydroxyvitamin D were adhered to for classifying the patients in terms of Vitamin D levels which are - Severe deficiency - <10ng/ml; Mild to moderate deficiency – 10-24.9 ng/ml; Optimal – 25-80 ng/ml; Possible toxicity - >80 ng/ml; Calcium reference levels used at our institute areNormal total calcium level 8.5 mg/dl – 10.5 mg/dl; Normal ionized calcium level 4.5-5.6 mg/dl.

Data collection

All enrolled patients of spontaneous aneurysmal SAH had these tests as part of their routine investigations during their treatment (conservative management or operative management).

Statistical analysis

All statistical calculations were conducted with standard statistical programs (IBM SPSS version 26) . Shapiro wilk test was applied to check the normality of variables that were included in the study. Parametric data was assessed with help of Student's T-test, one way ANOVA test. Non- Parametric data was analyzed with help of Chi Square, Mann Whitney U test, Kruskalwallistest. P-value of <0.05 was considered to be of statistical significance in the study.

Results

Out of 40 patients with aSAH, 18 were males (45%). 15 patients (37.5%) were in age group of 25-45 years, 16 (40%) were in age group of 46-60 years, 9 (22.5%) were in the age group of 61 -75 years. The mean age of patients was 51 years.

In our study 10 patients were current smokers (25%); 22 patients (55%) were hypertensive;and 14 patients (35%) were diabetic. The most common site of aneurysm was found to be anterior communicating artery (47.5%) and the least common was cerebellar artery (2.5%).

The study reported mean vitamin D level of 17.4 ± 7 ng/ml; mean calcium level 8.3 ± 0.9 mg/dl.

The study reported that out of 40 patients, 8 patients (20%) were severely deficient, 24 patients (60%) were mild to moderate deficient and 8 patients (20%) were having normal vitamin D levels. Amongst males, 61.1% were Vitamin D deficient whereas amongst females, 77.3% were deficient and this difference was found to be statistically insignificant (p-value=0.2).

Mean Vitamin D levels in males and females were 19.4 ± 6.7 ng/ml and 15.7 ± 7.0 ng/ml respectively. As Vitamin D levels in the study participants were found to be not normally distributed, therefore independent sample Mann-Whitney-U test was applied to check the mean difference of Vitamin D among gender and it was found to have no significant difference in the two groups (p-value = 0.106) (**Figure 1**).

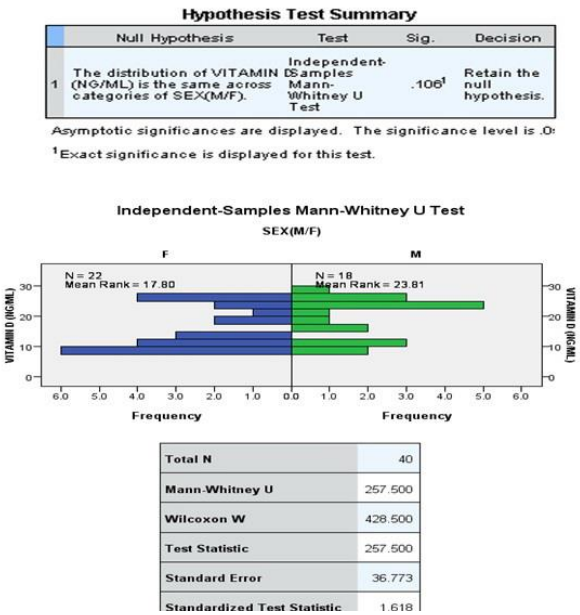

Figure 1. Independent sample Mann Whitney U test showing the mean difference of Vitamin D among gender.

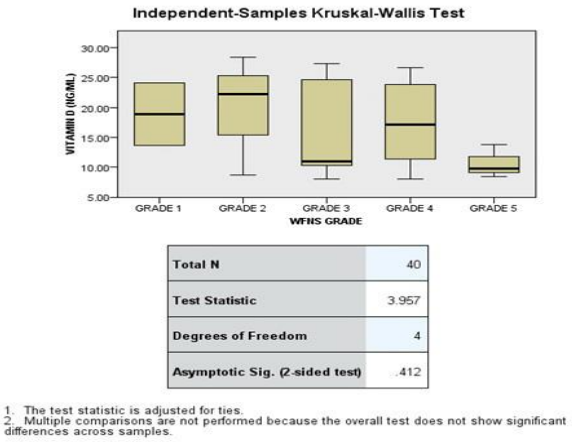

Figure 2. Kruskal Wallis test showing the mean difference of Vitamin D among WFNS Grade.

Mean Vitamin D level in smokers and non-smokers were 18.9 ± 7.1 ng/ml and 16.9 ± 7.0 ng/ml respectively and this difference was found to be non-significant, (p value - 0.45). Similarly, mean Vitamin D levels in Diabetics and Non-Diabetics; and Hypertensives and Non-hypertensives patient were 17.2 ± 6.6 ng/ml and 17.4 ± 7.4 ng/ml; and 17.3 ± 6.6 ng/ml and 17.4 ± 7.7 ng/ml respectively and these differences were found to be statisticallynon-significant (p value – 1 and 0.757 respectively) (**Table 1**).

Table 1. Mean Vitamin D levels in smokers - non-smokers, diabetics –non diabetics and hypertensive and normotensive patients.

Gender	No of patients	Mean (vitamin D)	SD	P value
Female	22	15.7	7.0	0.106
Male	18	19.4	6.7	
Smoking	No of patients	Mean (vitamin D)	SD	P value
No	30	16.9	7.0	0.45
Yes	10	18.9	7.1	
Diabetes mellitus	No of patients	Mean (vitamin D)	SD	P value
No	26	17.4	7.4	1.00
Yes	14	17.2	6.6	
Hypertension	No of patients	Mean (vitamin D)	SD	P value
No	18	17.4	7.7	0.757
Yes	22	17.3	6.6	

The mean vitamin D levels in the various WFNS grades (**Figure 2**), Modified Fischer grades and Hunt and Hess gradesof patients were found to be statistically non-significant using the Kruskal-Wallis test (p value =0.412, 0.568, 0.529 respectively) (**Table 2**).

Table 2. Vitamin D levels across WFNS grades, Modified Fischer grades and Hunt & Hess grades.

WFNS grades	**Mean (Vitamin D)**	**SD**	**P value**
I	18.9	7.4	0.412
II	20.4	7.0	
III	16.9	8.6	
IV	17.3	6.7	
V	10.7	2.8	
Modified FISCHER grades	Mean (vitamin D)	SD	P value
I	19.2	6.9	0.568
II	16.8	9.7	
III	15.7	6.0	
IV	17.7	7.1	
HUNT & HESS grades	Mean (vitamin D)	SD	P value
I	13.7	0	0.529
II	20.6	7.0	
III	19.7	8.0	
IV	15.5	8.0	
V	16.6	5.8	

The present study reported that half of the patients (n=20) were hypocalcaemic and the other half were normocalcaemic. Mean calcium levels in males and females were 8.5 ± 1.0 mg/dl and 8.2± 1.0 mg/dl respectively and this difference was not statistically significant (p value=0.3)

Similarly, the mean calcium levels in smokers and non-smokers; diabetics and non-diabetics; Hypertensives and Non-hypertensives were 8.4 ± 0.9 mg/dl and 8.3 ± 1.0 mg/dl;8.0 ± 0.9 mg/dl and 8.5 ± 1.0 mg/dl; 8.3 ± 0.9 mg/dl and 8.4 ± 1.0 mg/dl respectively and these differences were not statistically significant (p value=0.8, 0.07, 0.65) (**Table 3**).

Table 3. Mean serum calcium levels across gender, smokers - non-smokers, diabetics –non diabetics and hypertensive and normotensive patients.

Gender	**No of patients**	**Mean(calcium)**	**SD**	**P value**
Female	22	8.2	1.0	0.3
Male	18	8.5	1.0	
Smoking	No of patients	Mean(calcium)	SD	P value
No	30	8.3	1.0	0.8
Yes	10	8.4	0.9	

Diabetes mellitus	No of patients	Mean(calcium)	SD	P value
No	26	8.5	1.0	0.07
Yes	14	8.0	0.9	
Hypertension	No of patients	Mean(calcium)	SD	P value
No	18	8.4	1.0	0.65
Yes	22	8.3	0.9	

The mean serum calcium amongst the different WFNS grades did not differ statistically significantly (p value = 0.07) whereas the mean serum calcium levels were found to differ statistically significantly amongst the various Modified Fischer grades Hunt & Hess grades with p values 0.002 and 0.04 respectively (**Table 4**).

Table 4. Serum Calcium levels across WFNS grades, Modified Fischer grades and Hunt & Hess grades.

WFNS grades	**Mean(calcium)**	**SD**	**P value**
I	8.6	0.14	0.07
II	9.0	0.87	
III	8.3	1.3	
IV	8.2	0.83	
V	7.3	0.4	
Modified FISCHER grades	Mean(calcium)	SD	P value
I	9.0	0.8	0.002
II	8.9	0.4	
III	7.8	0.9	
IV	7.9	0. 9	
HUNT & HESS grading	Mean (calcium)	SD	P value
I	8.7	0	0.04
II	8.4	0.3	
III	8.8	1.4	
IV	8.6	0.7	
V	7.7	0.8	

Discussion

Despite recent advances in thediagnostic modalities, management and availability of plenty of literature, a substantial mortality as well as morbidity rate is attributable to unfavourable overall outcomes in patients following aSAH. Various factors have been implicated in occurrence and poor outcome in aSAH patients. However only handful of those have been found to reliably predict the incidence of aSAH . This study was designed to identify the mean serum Vitamin D and serum Calcium levels and its any association in aSAH patients.

The mean age of patients was 51 years. Weir et al[19]studied 945 patients of cerebral aneurysm and they found mean age of patients was 46 years. Aarhus et al[20]studied 444 patients of cerebral aneurysm and the median age of patients was 56 years . In our study out of 40 patients, 18 were males (45%) and 22 patients were females (55%) , which is comparable to the available literature suggesting that cerebral aneurysm is more common in females.

In our study 10 patients were chronic smoker (25%) and 30 patients (75%) were non smoker. 22 patients (55%) were hypertensive and 18 patients (45%) were non hypertensive. 14 patients (35%) were diabetic and 26 patients (65%) were non diabetic. Tuenissen et al[21]reviewed 9 longitudinal and 11 case control studies to identify the risk factors for aSAH and they found smoking ,hypertension and alcohol consumption were significantly related to the risk of spontaneous SAH .

We observed that the mean Vitamin D levels in males and females were 19.4±6.7 ng/ml and 15.7±7.0 ng/ml respectively and this difference was not statistically significant (p value=0.106). In our study in males, 61.1% were Vitamin D deficient whereas in females, 77.3% were deficient and however this difference was not statistically significant (p value=0.2). Guan J et al[10]in a retrospective study found the mean serum vitamin D level in patients with aneurysm was 23.3± 12.3 ng/ml whereas control group had mean level of 28.7± 14.1 ng/ml which was statistically significant .They used multivariable poisson regression and backward elimination to identify the risk factors .They found patients in the aneurysm group were older ,mostly females ,tobacco users ,hypertensive and had hypovitaminosis D but race ,body mass index and diabetes were not significantly different.

There was no statistically significant difference in mean vitamin D levels across WFNS grading (p value = 0.412) , Modified Fischer grading (p value = 0.568) and HUNT & HESS grading (pvalue-0.529).

We noted that the mean serum calcium level in males and females was 8.5 ± 1.0 mg/dl and 8.2 ± 1.0

mg/dl respectively and this difference was not statistically significant (p value=0.3).In our study 9 male patients and 11 female patients had calcium deficiency and it was not statistically significant (p value =1.0). Anil Can et al[22]did a multivariate analysis of serum calcium and magnesium levels to see the association with the ruptured aneurysm and they found hypomagnesemia and hypocalcemia were significantly associated with ruptured aneurysms.

In our study there was no significant difference in mean calcium levels across WFNS grades (p value = 0.07) (**Figure 3**). However, we found significant difference in mean calcium levels across Modified Fischer grades (p value = 0.002) and HUNT & HESS grades (p value=0.04) (**Figure 4**) which means low serum calcium level was associated with the higher grades.

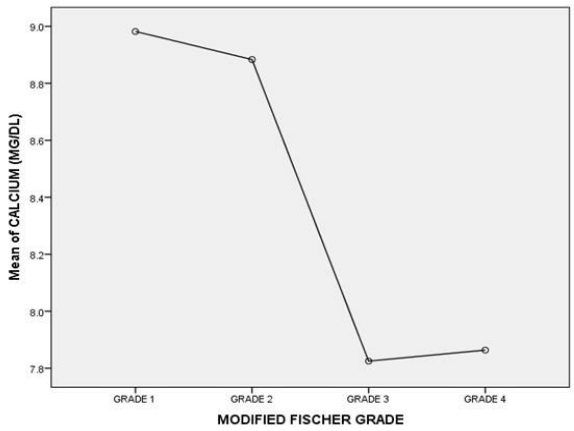

Figure 3. One-way Anova test showing the mean difference of calcium among WFNS Grade.

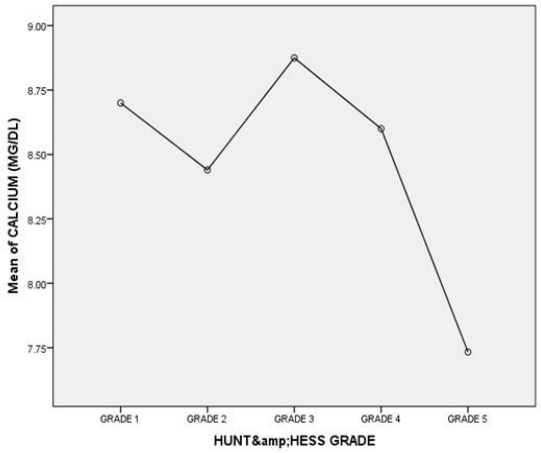

Figure 4. One-way Anova test showing the mean difference of calcium among HUNT & HESS Grading.

Van Heuven et al[23]in a retrospective study validated the prognostic value of WFNS grading on admission in determination of the outcome . Lindvall et al[24]found a significant correlation of Fischer scale and Hunt & Hess scale with the outcome of patient although the predictive value of limited due to low sensitivity and specificity of these scales .

We observed that the serum calcium has moderate positive correlation with Vitamin D and GCS . This correlation was statistically significant with a p value of 0.006 which explains the direct effect of serum vitamin D level in calcium absorption and its metabolism.

Conclusion

Aneurysmal subarachnoid hemorrhage is associated with high mortality and morbidity. We observed higher incidence of serum Vitamin D and serum Calciumdeficiencyin aSAHpatients .We found statistically significant difference in mean calcium levels across Modified Fischer grades (p value = 0.002) and HUNT & HESS grades (p value=0.04) .However further studies need to be undertaken to evaluate the role of Vitamin D and serum Calcium in aSAH. Also studies with a control group could help further validate this data.

Conflict of Interest

The authors have no conflict of interest to declare.

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References

1 De Rooij, N.K., Linn, F.H.H., van der Plas, J.A., Algra, A., Rinkel, G.J.E. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J NeurolNeurosurg Psychiatry. 2007;78:1365–1372.

2 Ingall T, Asplund K, Mahonen M, Bonita R. A Multinational Comparison of Subarachnoid Hemorrhage Epidemiology in the WHO MONICA Stroke Study. Stroke. 2000;31:1054-1061.

3 Van Gijn J. Subarachnoid haemorrhage: diagnosis, causes and management. Brain. 2001;124:249-278.

4 Suarez J, Tarr R, Selman W. Aneurysmal Subarachnoid Hemorrhage. New England Journal of Medicine. 2006;354:387-396.

5 Risselada R, de Vries L, Dippel D, van Kooten F, van der Lugt A, Niessen W et al. Incidence, treatment, and case-

fatality of non-traumatic subarachnoid haemorrhage in the Netherlands. Clinical Neurology and Neurosurgery. 2011;113:483-487.

6 Bansal M , Mittal R S .Clinical Demographic Association and Outcome in Patients with Aneurysmal Subarachnoid Hemorrhage.Indian J Neurosurg2015;4:63–68.

7 Timour Al-Khindi, R Loch Macdonald, Tom A. Schweizer. Cognitive and Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. Stroke. 2010;41:519-536.

8 Preiss M, Netuka D, Koblihova J, Bernadova L. Quality of life 1 year after aneurysmal subarachnoid hemorrhage in good outcome patients treated by clipping or coiling. Journal of neurological surgery, Central European neurosurgery. 2012;73:217-23.

9 Lai PM, Dasenbrock H, Du R. The Association between Meteorological Parameters and Aneurysmal Subarachnoid Hemorrhage: A Nationwide Analysis. PLoS One. 2014;9:112961.

10 Guan J, Karsy M, Eli I, Bisson EF, McNally S, Taussky P, Park MS. Increased Incidence of Hypovitaminosis D Among Patients Requiring Treatment for Cerebral Aneurysms. World Neurosurgery. 2016;88:15-20.

11 Alvarado Y, Perez A. Effects of Vitamin D deficiency in aneurysmal subarachnoid hemorrhage. Critical Care Medicine. 2015;43:138 .

12 Chung PW, Park KY, Kim JM, Shin DW, Park MS, Chung YJ, et al. 25- hydroxyvitamin D status is associated with chronic cerebral small vessel disease. Stroke. 2015;46:248-251.

13 Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, et al. Reduced vitamin D in acute stroke. Stroke. 2006;37:243-245.

14 Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med. 2008;168:1174- 1180.

15 Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503-511.

16 Wong YY, Flicker L, Yeap BB, McCaul KA, Hankey GJ, Norman PE. Is hypovitaminosis D associated with abdominal aortic aneurysm, and is there a dose-response relationship? Eur J VascEndovasc Surg. 2013;45:657-664.

17 Kassi E, Adamopoulos C, Basdra EK, Papavassiliou AG. Role of vitamin D in atherosclerosis. Circulation. 2013;128:2517-2531.

18 Inoue Y, Miyashita F, Toyoda K, Minematsu K. Low serum calcium levels contribute to larger hematoma volume in acute intracerebral hemorrhage. Stroke. 2013;44:2004–2006. doi: 10.1161/STROKEAHA.113.001187.

19 Weir B. Unruptured intracranial aneurysms: a review. J Neurosurg. 2002;96:3–42.

20 Aarhus, M., Helland, C.A. & Wester, K. Differences in anatomical distribution, gender, and sidedness between ruptured and unruptured intracranial aneurysms in a defined patient population. ActaNeurochir 151, 1569 (2009).

21 Teunissen LL, Rinkel GJ, Algra A, van Gijn J. Risk factors for subarachnoid hemorrhage: a systematic review. Stroke1996; 27: 544–9.

22 Can A, Rudy RF, Castro VM, Dligach D, Finan S, Yu S, Gainer V, Shadick NA, Savova G, Murphy S, Cai T, Weiss ST, Du R. Low Serum Calcium and Magnesium Levels and Rupture of Intracranial Aneurysms. Stroke. 2018 Jul;49(7):1747-1750. doi: 10.1161/STROKEAHA.118.020963.

23 Van Heuven A, DorhoutMees S, Algra A, Rinkel G. Validation of a Prognostic Subarachnoid Hemorrhage Grading Scale Derived Directly From the Glasgow Coma Scale. Stroke. 2008;39(4):1347-13.

24 Lindvall P, Runnerstam M, Birgander R, Koskinen L. The Fisher grading correlated to outcome in patients with subarachnoid haemorrhage. British Journal of Neurosurgery. 2009;23(2):188-192.