Original Article

Association of Bone Mineral Density, Vitamin D, and Serum Calcium in Intracranial Aneurysm

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Abstract

Aims: The objective of this study is to understand the association between bone mineral density (BMD), serum calcium, and Vitamin D in s (IA) patients. **Subjects and Methods:** A total of 100 patients with IA diagnosed at the department of neurosurgery between January 2019 and December 2019 were reviewed and analyzed in this study. Computed tomography angiography was used to confirm and locate the site of aneurysms. BMD, serum calcium, and Vitamin D levels were measured. **Statistical Analysis Used:** Linear or logistic regression statistical models were applied to found the association between BMD and IA size. To confirm the statistical significance, $P < 0.05$ (twos-tailed) was considered as statistically significant. **Results:** Of the studied 100 patients, 61 patients were female and 39 were male. According to the age group, patients were divided into five categories: below 30, 31–40, 41–50, 51–60, and ≥60 years. The most common site of aneurysm observed to be the anterior communicating artery (Acom); 39.25% of the patients had Acom aneurysm followed by the middle cerebral artery (18.69%). This clearly shows that the occurrence of aneurysm is more prominent in anterior circulation as compared to posterior circulation. The results showed that there is a negative linear correlation between BMD and size of aneurysm ($P = 0.00043$, $r = -0.12$). Sex-specific analysis showed that females have lower mean BMD value as compared to males (i.e., females 0.785 ± 0.13; males 0.887 ± 0.13; $P = 0.0003$). We also found that the multiplicity of IAs also shows an association with BMD (i.e. mean BMD: 0.825 ± 0.14, whereas BMD of patients with multiple aneurysms was 0.747 ± 0.08; $P = 0.05$). Of 100 patients, 66 were observed calcium deficient (normal range: 8.8–10.2 mg/dl). The obtained mean value of calcium was 8.56 ± 0.859 standard deviation (SD), i.e., below the normal range of calcium. In the case of Vitamin D, 85% of the patients were observed Vitamin D deficient, whereas 14 patients showed Vitamin D insufficiency and merely 1 patient has Vitamin D sufficiency. The mean 25-hydroxy Vitamin D level obtained in our study was 14.57 ± 5.60 (SD), which is considered as Vitamin D deficiency. **Conclusions:** The size and multiplicity of IA can be associated with BMD, calcium, and Vitamin D. The results from the research provide evidence of common pathophysiology between the development of IA and these factors.

Keywords: *Bone mineral density, calcium, intracranial aneurysm, Vitamin D*

Introduction

An intracranial aneurysm (IA) is an abnormal focal dilation within the wall of an artery in the brain that leads to an irregular widening or ballooning, with an occurrence of approximately 2%–4%. Most unruptured IAs (90%) are asymptomatic and are <10 mm in size. Nevertheless, the resulting bleeding into spaces around the brain called as subarachnoid hemorrhage (SAH) can lead to coma or stroke.[1] In most cases, the exact cause of IA is not known except in mycotic and traumatic aneurysm. IA is associated with several factors such as hypertension, atherosclerosis, inherited family genetics, smoking, trauma, and infection.[2] Inherited risk factors associated with aneurysm include pseudoxanthoma elasticum, fibromuscular dysplasia, hereditary hemorrhagic telangiectasia, coarctation of the aorta, and Ehlers–Danlos syndrome. Usually, there are no prevailing symptoms of IA until it ruptures. Diagnosis and monitoring of IAs can be done using computed tomography or computed tomography angiography (CTA),[3] magnetic resonance imaging, magnetic resonance angiography, digital subtraction angiography (DSA), and transcranial Doppler ultrasonography. Treatment of IA

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will be determined by considering various factors including age, overall health, size of aneurysm, medical history, location of the aneurysm, and extend of the disease. Two major surgical procedures were used in the treatment of IA consisting of endovascular coiling and surgical clipping.[4,5] Although various diagnoses and treatment for SAH are available, mortality and disability associated with SAH remain high in untreated cases.

Low bone mineral density (BMD) has been reported as an independent indicator for cardiovascular mortality, and osteoporosis and associated fractures in cardiovascular disease patients are more frequent.[6] In a recent article, Shin *et al*. showed that the occurrence, size, and multiplicity of IA can be related to BMD.[7] The study shows evidence of shared pathophysiology between bone fragility and IA. Researchers concluded that a decrease BMD in the lumbar spine, femoral neck, and hip is related with increased chances of IA. The researchers suggested that "local hemodynamic stress and inflammatory response on arterial wall along with pathologic extracellular matrix remodeling," could be a plausible explanation for the above-mentioned association.

In a recent finding, it has been established that Vitamin D deficiency leads to acute stroke.[8] Vitamin D level is also associated with chronic cerebral small-vessel disease.[9] It has therefore been identified that the inadequacy of Vitamin D associated with low BMD contributes to the coronary artery calcification and dramatically increases cardiovascular disease. In the latest article by Guan *et al*.,[10] a correlation has been identified between Vitamin D deficiency with cerebral aneurysms and aneurysmal SAH. Researchers analyze the frequency of hypovitaminosis D in patients with cerebral aneurysms requiring surgical or endovascular intervention and find that hypovitaminosis D is substantially higher in patients with cerebral aneurysms. Apart from BMD and hypovitaminosis D, serum calcium also plays an important role in IA. Studies suggest a strong correlation between serum calcium levels and patients with acute intracerebral hemorrhages.[11] The major cause for this could be impaired hemostasis caused by hypocalcemia and hypomagnesemia.[12] In this study, we attempted to associate the relation between BMD, serum calcium, and Vitamin D in IA patients.

Subjects and Methods

A prospective study has been conducted on 100 patients admitted with radiological evidence of IA at the department of neurosurgery during January–December 2019. The patients were incorporated in the study after obtaining written and informed consent. All age group patients were included in the study. Cancer patients; patients of known kidney disease, endocrinal disorder, and bone diseases; and patients taking calcium or Vitamin D supplement or on steroid treatment were excluded from the study. CTA was used to confirm and locate the site of aneurysms. The results were further confirmed using DSA. Aneurysmal size was defined as the maximum measurement from the neck to the tip of the aneurysm dome among the largest diameter. In case of multiple aneurysms, the largest aneurysm (in diameter) was considered in the study along with the number of aneurysm. Dual-energy X-ray Absorptiometry (DEXA Scan using DEXA Explorix ADS) has been used for assessing BMD at the lumbar vertebra (L1 to L4). In a recent study,[9] the authors assessed BMD at three different regions: lumbar vertebrae (L1 to L4), femur neck, and total hip, and the strongest correlation was obtained in the lumbar spine region. Therefore, herein, we studied the BMD at the lumbar spine region. All measurements were done using standardized procedures. As per the WHO standards, BMD classified into three categories on the basis of T score: T score ≥−1 standard deviation (SD) (normal), T score between −1 and −2.5 SD (osteopenia), and T score ≥−2.5 SD (osteoporosis). It is important to mention here that all studies were done exclusively on the confirmed IA patients and no control cases are included in the work. Linear or logistic regression models were applied to found the association between the BMD and IA size. To confirm the statistical significance, $P < 0.05$ (two-tailed) was considered as statistically significant.

Blood tests were drawn for the assessment of serum calcium and 25-Hydroxy Vitamin D in IA patients. In our study, serum calcium was calculated using spectrophotometer (Beckman Coulter AU680) utilizing a calcium sensitive dye (reagent kit [ARSENAZO III]). Concentration of total serum calcium in the range between 8.8 and 10.2 mg/dL is considered as normal and the levels below this are considered as hypocalcemia. The serum 25-Hydroxy Vitamin D level was measured using chemiluminescent immunoassay (Advia Centaur XP). According to the Vitamin D levels, patients were divided into three groups: deficiency <20; insufficiency: 20–30; and sufficient: 30–100 ng/ml.

Results

First of all, population characteristics were determined. Of the studied 100 patients, 61 patients were female and 39 were male. The bar diagram is shown in Figure 1a. According to the age group, patients were divided into five categories: below 30, 31–40, 41–50, 51–60, and ≥60 years, as shown in Figure 1b. From [Figure 1b], we can see that very few patients were below 30 years and maximum patients were 50–60 years. The results clearly show that maximum aneurysm patients are above 40 years with a mean age of 51.63 (±11.3).

Distribution of the aneurysm sites is shown in Figure 2a. The most common site of aneurysm observed to be the anterior communicating artery (Acom); 39.25% of the patients had Acom aneurysm. The second common site of aneurysm is the middle cerebral artery (18.69%), followed

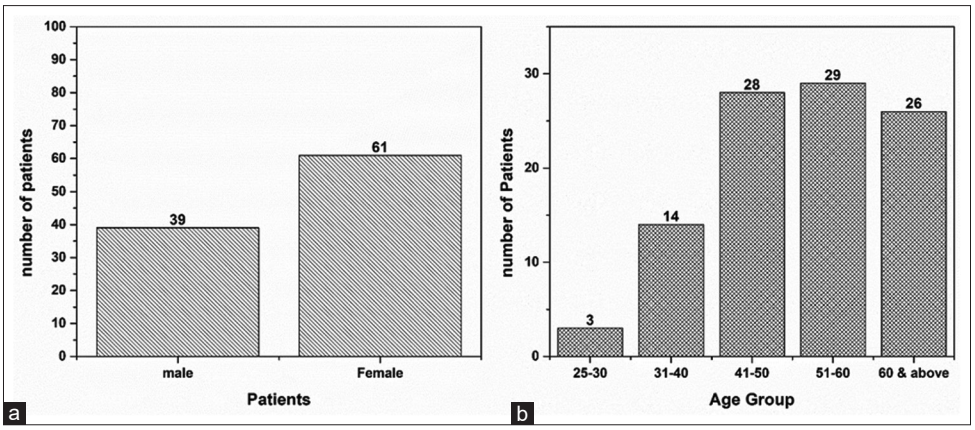

Figure 1: (a) Bar diagram showing female and male population. (b) Intracranial aneurysm patients divided by the age group

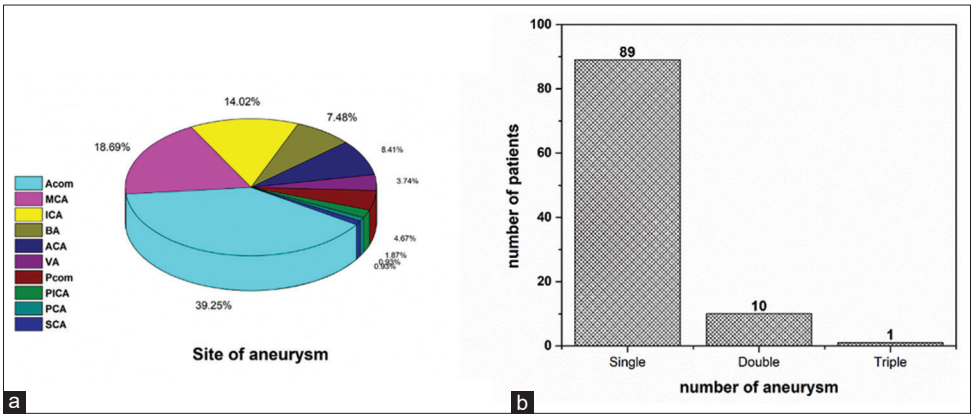

Figure 2: (a) Locations (site) of the aneurysms; (b) multiplicity of aneurysm

by the internal carotid artery (14.02%), anterior cerebral artery (8.41%), basilar artery (7.48%), and posterior communicating artery (4.67%). Vertebral artery, posterior inferior cerebellar artery, posterior cerebral artery, and superior cerebellar artery had 3.74%, 1.87%, 0.83%, and 0.83% incidence, respectively. This clearly shows that the occurrence of aneurysm is more prominent in anterior circulation as compared to posterior circulation.

Of 100 patients, single aneurysm was observed in 89 patients, whereas 11 patients showed multiple aneurysms. Ten patients have double aneurysm and one patient had triple aneurysm, as shown in Figure 2b. In this study, we did not found any correlation between the multiplicity of IA and sex.

From our study, we found that out of 100 patients, 53 patients showed osteopenia, whereas 35 patients had osteoporosis, as shown in Figure 3a. Furthermore, from 35 osteoporosis patients, 71.42% were female. This suggests that both osteoporosis and IA are diseases predominant in women. We have also attempted to identify the correlation between BMD and aneurysm size and multiplicity. Our results [Figure 3b] showed that there is a negative linear correlation between BMD and size of aneurysm (P = 0.00043, r =−0.12). Sex-specific analysis showed that females have lower mean BMD value as compared to males (i.e. females: 0.785 ± 0.13; males: 0.887 ± 0.13; P = 0.0003). Interestingly, we found that the multiplicity of IAs also shows an association with BMD (i.e., mean BMD: 0.825 ± 0.14), whereas BMD of patients with multiple aneurysm shows value of 0.747 ± 0.08 (P = 0.05). Tis means, the risk of multiplicity of aneurysm as well as the size of aneurysm increases as BMD decreases.

In our study, 100 patients, 66 were observed calcium deficient (normal range: 8.8–10.2 mg/dl). The obtained mean value of calcium was 8.56 ± 0.859 (SD), i.e., below the normal range of calcium [Figure 4a]. In the case of Vitamin D, 85% of the patients were observed Vitamin D deficient, whereas 14 patients showed Vitamin D insufficiency and merely one patient has Vitamin D sufficiency [Figure 4b]. Mean 25-hydroxy Vitamin D level obtained in our study was 14.57 ± 5.60 (SD) which is considered as Vitamin D deficiency.

Discussion

From the literature, it has been known that low BMD is related to IA and also with a larger size of aneurysm.[7] We have also found similar results where patients have large

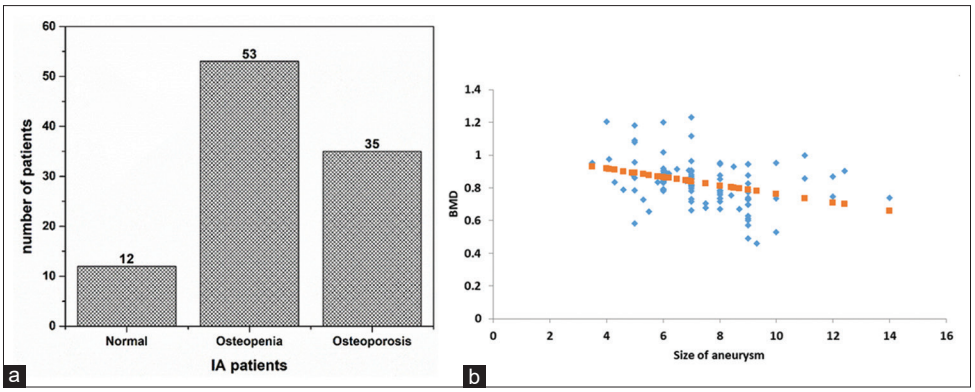

Figure 3: (a) Intracranial aneurysm patients divided into osteopenia, osteoporosis, and normal categories. (b) Relation between bone mineral density values and size of intracranial aneurysm

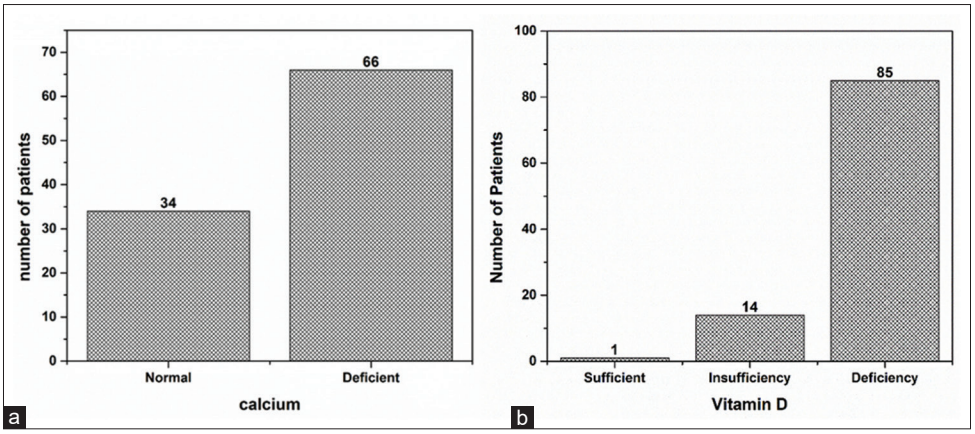

Figure 4: (a) Number of patients divided on the basis of calcium levels. (b) Patients divided on the basis of Vitamin D levels

IA and have low BMD. A low BMD is also associated with the multiplicity of IA. Sex-specific analysis showed a low BMD in females as compared to males.

Although it remains to be established, the precise pathogenesis of cerebral aneurysm formation, growth and rupture, extracellular matrix (ECM) defects and degeneration, hemodynamic stress, and inflammatory responses are suggested as key components resulting in structural fragility within the arterial wall.[13]

A lower BMD is associated with having a brain aneurysm, thus indicating a shared pathophysiology between the two. The reason for this association is often explained as "local hemodynamic stress and inflammatory response on arterial wall along with pathologic ECM remodelling," the researchers suggested.[14] ECM components, such as collagen and nonproteins, also form the organic part of the bone matrix.[15] Changes in the aneurysm wall, in particular focal degradation of the ECM and matrix degrading proteases, were linked to the formation and growth of aneurysm.[16]

Lysyl oxidase (LOX) catalyzes elastin and collagen cross-linking and regulates the interlinking and maturing of elastin and collagen fibers. In a study of homogeneous, Korean population researchers investigated the association between IA formation and LOX gene polymorphisms.[17] Authors studied ten single-nucleotide polymorphisms (SNPs), of which three SNPs were identified which plays a significant role in the formation of IA ($P < 0.01$).

Our results showed that out of osteoporosis patients, maximum were females. Both osteoporosis and IA are more common in females according to our findings and literature; hence, it is possible that the pathophysiological process of the both diseases is associated with sex hormones.

Mice studies have shown that estrogen plays a central role in vascular biology; it increases endothelial cell function and leads to nitric oxide discharges. Estradiol also affects functioning of smooth muscle cells and collagen degradation and decreases the development of abdominal aortic aneurysms. Jamous *et al*.[18,19] have highlighted the role of estrogen deficiency in cerebral aneurysm formation and progression. Authors have experimentally shown that bilateral oophorectomy increases the vulnerability of IA formation in female rats; hence, administration of sustained-release 17-β estradiol pellets reduces the incidence of IA development. This suggests that hormones play a significant role in cerebral aneurysm pathogenesis.

Experimental studies showed that female sex has an association with IA formation.[20] Studies have also shown a correlation between female sex and multiplicity of aneurysm.[20] However, we did not find such a correlation.

In our study, 85% of the population showed Vitamin D deficiency which suggests a relationship between IA and Vitamin D level. Although our 55% of the population are above 50 years [Figure 1b], we did not find any correlation between age and Vitamin D levels. Similar results were obtained by Guan *et al*.[10] where authors examined the association between hypovitaminosis D and IA. The researchers explained this association as Vitamin D influences a wide range of metabolic processes by genomic and nongenomic pathways that affect properties of peripheral artery and affect vessel development and remodeling.[21] In addition, Vitamin D has been shown to have antiproliferative effects on smooth muscle cells in the arterial walls[22] moreover regulates the immune response of the body.[23,24] Experimental data shown that patients having cerebral aneurysms have increased incidence of hypovitaminosis D and a high prevalence of SAH patients with Vitamin D deficiency. Furthermore, females show lower mean Vitamin D value as compared to males (P = 0.025) which shows a major association between Vitamin D level and sex hormones.[25]

In our study, we found that 66% of the IA patients were calcium deficient which suggests that calcium plays a significant role in IAs. Calcium is a crucial cofactor in coagulation cascade and plays a significant role in intracerebral hemorrhage pathophysiology. Hypocalcemia and hypomagnesemia cause impaired hemostasis which cause bleeding in intracerebral hemorrhage patients.[26] Another possible mechanism by which hypocalcemia could lead to SAH is vasoconstriction and subsequent elevation of blood pressure by affecting vascular reactivity.

In this work, we analyzed and attempted to correlate various factors responsible for IA such as BMD, serum Vitamin D, and serum calcium levels. Furthermore, we tried to establish the relationship between sex hormones and IA. According to our knowledge, this is the first study to evaluate all these factors together. The main limitation of our work is its cross-sectional design and the lack of control cases. This study only analyzes and associates the relationship between IA, BMD, Vitamin D, and calcium at the time of evaluation, and no pre- and post-follow ups were done. We hope that a detailed prospective follow-up study can evaluate the relationship between these factors and aneurysm.

Conclusions

In this prospective study, we found that low BMD, low serum calcium, and hypovitaminosis D are associated with the occurrence of IAs. BMD seems to have a negative association with aneurysm size. Furthermore, low BMD is associated with the multiplicity of IA. Sex-specific analysis showed that females have lower BMD values as compared to males. Furthermore, among osteoporosis population, maximum were females. These results suggest that the pathophysiological process of the both diseases is associated with sex hormones. We also obtained that majority of the IA population are Vitamin D deficient which suggests the association of hypovitaminosis D with IA. Similarly, 66% of the population is calcium deficient. These results suggest a significant association between BMD, Vitamin D, and serum calcium with IA. This study opens new avenue in the field of IA and further prospective investigations can help in understanding the pathophysiology of IAs.

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Conflicts of interest

There are no conflicts of interest.

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