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Original research article

Gender specific association of decreased bone mineral density in patients with epilepsy



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ARTICLE INFO

Article history:

Received 23 February 2015

Accepted 11 June 2015

Available online 22 June 2015

Keywords:

Epilepsy

Bone mineral density

X-ray absorptiometry

Antiepileptic drugs

ABSTRACT

Objective: To evaluate whether epilepsy or certain antiepileptic drugs render patients prone to develop low bone mineral density (BMD) and osteoporosis risk.

Methods: Thirty-eight (27 males, 11 females) consecutive adult epileptic patients receiving antiepileptic drugs (AEDs) and 71 control individuals matched for race, gender, age and body mass index (BMI) were subjected to dual energy X-ray absorptiometry (DXA).

Results: The mean lumbar spine and total hip BMD values were lower in the patients compared to control group ($0.90 \pm 0.24 \text{ g/cm}^2$ vs $1.04 \pm 0.14 \text{ g/cm}^2$, $p < 0.001$ and $0.92 \pm 0.14 \text{ g/cm}^2$ vs $0.99 \pm 0.13 \text{ g/cm}^2$, $p = 0.02$, respectively). At the same skeletal sites, male patients had significantly reduced BMD compared to control males ($0.90 \pm 0.21 \text{ g/cm}^2$ vs $1.03 \pm 0.15 \text{ g/cm}^2$, $p = 0.004$ and $0.93 \pm 0.14 \text{ g/cm}^2$ vs $1.02 \pm 0.13 \text{ g/cm}^2$, $p = 0.009$, respectively) while there was a trend but no significant differences in females. This BMD reduction was independent of AED type.

Conclusion: Adult epileptic, predominantly male patients have lower BMD and could be screened with densitometry for early diagnosis and prevention of osteoporosis.

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1. Introduction

Low bone mineral density (BMD) is rare in young adults and either occurs in pregnant females as transient osteoporosis [1,2] or in both sexes in certain diseases such as multiple

sclerosis [3,4], chronic glucocorticoid administration or immobility [4], stroke [5], and epilepsy [6,7].

Epileptic patients may exhibit low BMD possibly as a side effect of certain antiepileptic drugs (AEDs) use, even in children below 18 years old [6]. AEDs can be categorized into three broad groups in accordance to their property to induce,

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inhibit or not induce/inhibit liver enzymes, such as the cytochrome P450 2C19 (CYP2C19), that metabolize various drugs, including clopidogrel and several AEDs: the first group includes the enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and primidone, the second group consists of the enzyme inhibitor VPA, and the third group consists of enzyme non-inducers/inhibitors such as clonazepam, ethosuximide, gabapentin, lacosamide, lamotrigine, pregabalin, tiagabine, and zonisamide. It has been suggested that the AEDs with hepatic enzyme induction properties may exercise a negative effect on BMD in comparison to non-inducer AEDs. Furthermore, valproate may negatively influence BMD [8]. Thus, valproic acid monotherapy may be a cause for low BMD in epileptic patients according to Sato et al. [9]; however, Triantafyllou et al. did not observe any relation of long term valproate monotherapy with reduced BMD [10].

There have been controversial studies concerning gender, with either reporting lower BMD in epileptic males than females, or equally reduced BMD in both gender [7,11,12]. In any event, the associations of gender and AEDs with BMD are still unresolved in epilepsy and deserve further investigation [10,13]. The objective of the present case-control study was to evaluate the BMD at certain skeletal sites of adult epileptic patients and its potential association with gender and AED type.

2. Patients and methods

2.1. Participants

Thirty-eight (27 males, 11 females) adult epileptic patients on various AEDs and 71 race, gender, age and BMI matched controls were subjected to DXA scanning. Epileptic patients were adults, receiving AEDs for more than 1 year, as described below. Patient data, including gender and age, body mass index (BMI), length of exposure to AEDs and AEDs type, were recorded. The control group included 71 healthy non-relative visitors to hospitalized patients. Smoking, either active or ceased within the last 6 months, was recorded as current for all participants and BMI was calculated. Participants with BMI higher than 40 kg/m², on corticosteroids, bisphosphonates or selective estrogen receptor modulators use and/or with a medical condition or metallic implants, that influence DXA values, were excluded.

According to the number and type of AEDs administrated, patients were further sub-grouped: Group A included patients on AEDs with either weak or no CYP2C19 inducing or inhibiting properties (lamotrigine, levetiracetam, oxcarbamazepine, tomiramate or/and gabapentin); Group B included patients on AEDs with CYP2C19 inducing properties, as phenytoin (PHT), carbamazepine (CBZ) and/or phenobarbital (PB) on monotherapy or polytherapy; Group C included patients receiving valproic acid (VPA), a known CYP2C19 inhibitor, with or without concurrent AEDs having no inducing or inhibiting properties; Group D included patients taking or having taken a combination of AEDs with enzyme-inducing properties (CBZ, PHT, PB) and VPA.

The study protocol was in compliance with the Helsinki Declaration and an informed consent was signed by all participants.

2.2. Scanning

DXA scanning was performed utilizing a Hologic Discovery W scanner (Hologic, Bedford, MA, USA). All patients had DXA scans performed in the supine position, in both the lumbar spine (L1-L4) and left hip. The scans and data analysis were performed by the same technician. For data analysis, a software package (v.12.3.7; Hologic, Bedford, MA, USA) was employed as directed by the manufacturer.

2.3. Statistical analysis

Multivariate regression analysis was performed after adjustment for gender, age, BMI, smoking, length of exposure to AEDs and AEDs type. For statistical analysis, epileptic patients were studied in four subgroups according to their AEDs as mentioned above. Statistical analysis was undertaken using SPSS 20.0 for windows. *P* values less than 0.05 were considered significant.

3. Results

Thirty-eight ambulatory adult outpatients (27 males, 11 females) with epilepsy were recruited in the study. Patients and control group physical characteristics are depicted in Table 1.

The mean lumbar spine and total hip BMD values were significantly lower in the patient group than the control group (0.90 ± 0.24 g/cm² versus 1.04 ± 0.14 g/cm², *p* < 0.001 and 0.92 ± 0.14 g/cm² versus 0.99 ± 0.13 g/cm², *p* = 0.02, respectively) while no statistically significant difference was found for femoral neck BMD (Table 2).

Age, BMI and smoking were significantly associated with every mean BMD value. Further multivariate regression analysis with adjustment for age, BMI and smoking showed that lumbar spine mean BMD, but not total hip mean BMD, was significantly decreased (*p* = 0.001) in the patient compared to control group. Epilepsy duration was not significantly associated with any of the mean BMD values in the patient group.

Table 1 – Characteristics of the patients and control group individuals.

| Characteristics | Patients (38) | Controls (71) | <i>p</i> |
|----------------------------------|---------------|---------------|----------|
| Gender | 27 M/11 F | 49 M/22 F | 0.82 |
| Mean age, years | 38.2 ± 12.3 | 38.9 ± 10.4 | 0.74 |
| Males | 39.04 ± 13.4 | 40.08 ± 10.7 | 0.71 |
| Females | 36.1 ± 8.9 | 36.3 ± 9.3 | 0.94 |
| BMI (kg/m ²) | 26.01 ± 4.8 | 26.1 ± 3.7 | 0.85 |
| Males | 26.2 ± 4.7 | 27.1 ± 3.2 | 0.25 |
| Females | 25.7 ± 5.3 | 23.9 ± 3.9 | 0.27 |
| Smoking (%) | 14 (36.8%) | 44 (61%) | 0.01 |
| Males | 11 (40.7%) | 30 (61.2%) | 0.07 |
| Females | 3 (27.2%) | 14 (63.6%) | 0.05 |
| Median E duration, years (range) | 10 (1–40) | | |
| Males | 12 (1–40) | | |
| Females | 6 (1–35) | | |

M: males; F: females; E: epilepsy; BMI: body mass index; BMD: bone mineral density.

Table 2 – Bone mineral density results of the patients and control group individuals.

| DXA results | Patients (38) | Controls (71) | p |
|------------------|---------------|---------------|---------|
| Lumbar spine BMD | 0.90 ± 0.24 | 1.04 ± 0.14 | <0.001* |
| Males | 0.90 ± 0.21 | 1.03 ± 0.15 | 0.004* |
| Females | 0.90 ± 0.32 | 1.06 ± 0.11 | 0.052 |
| Total hip BMD | 0.92 ± 0.14 | 0.99 ± 0.13 | 0.02* |
| Males | 0.93 ± 0.14 | 1.02 ± 0.13 | 0.009* |
| Females | 0.92 ± 0.15 | 0.94 ± 0.14 | 0.69 |
| Femoral neck BMD | 0.81 ± 0.15 | 0.85 ± 0.13 | 0.09 |
| Males | 0.80 ± 0.16 | 0.87 ± 0.13 | 0.06 |
| Females | 0.81 ± 0.14 | 0.82 ± 0.14 | 0.85 |

BMD: bone mineral density (mean value ± standard deviation); DXA: X-ray absorptiometry; males: N = 27; females: N = 11.

* Statistically significant.

Regarding gender, lumbar spine and total hip BMD values were significantly lower in male patients than male controls ($0.90 \pm 0.21 \text{ g/cm}^2$ vs $1.03 \pm 0.15 \text{ g/cm}^2$, $p = 0.004$ and $0.93 \pm 0.14 \text{ g/cm}^2$ versus $1.02 \pm 0.13 \text{ g/cm}^2$, $p = 0.009$, respectively) but no statistical difference was noted in females, except for a trend for lower BMD only in lumbar spine. No significant difference regarding femoral neck mean BMD was found in either gender (Table 1).

Further comparisons of lumbar spine, total hip and femoral neck BMD were conducted in different AED groups. Noteworthy, the lumbar spine BMD was lower in Group A patients (lamotrigine, levetiracetam, oxcarbamazepine, tomiramate and/or gabapentin) with levetiracetam being the most common AED used on monotherapy or polytherapy (2 and 5 patients accordingly), while the total hip and femoral neck BMD were lower in Group B patients, but no difference reached statistical significance (Table 3). Similar results were found in males, with the lowest BMD noted in the lumbar spine of Group A patients but not reaching statistical significance. Comparisons among females were not possible due to the small sample size.

4. Discussion

Several neurological diseases have been associated with low BMD [3,4,14–16,5,17,18]. Among them, epilepsy is a neurological condition of interest due to the presence of seizures that

may cause increased frequency of bone fractures in up to 33.9% of epileptic individuals [19–21]. In 87 epileptic patients on phenytoin, the 7 years occurrence of non-seizure-related fractures was six times more frequent compared to normal population [22]. The peak period of all fractures in epileptic patients has been reported between 40 and 49 years of age [20]. In accordance with most studies, our results demonstrated low BMD in epileptic patients, in both lumbar spine and a total hip. As it was found in our study (Table 2), male preponderance was reported in other studies of chronic antiepileptic use in young adult patients and low BMD [7].

In a study from England including 208 institutionalized patients, bone disease affected mainly young, male patients [23], while in a young adult study male gender was a risk factor for low BMD at the spine of epileptic patients [7]. In our study all but one female were pre-menopausal. The presence of estrogens during the pre-menopausal period, contributing to the maintenance of skeletal homeostasis and the apoptotic death in osteoclasts [24], potentially explain the gender-related findings in studies implicating young epileptic adults, as the present study.

Apart from the diagnosis of epilepsy, the AEDs have been accused as risk factors for low bone density [25] and fractures [19,21]. It has been suggested that the mechanism of action of antiepileptic drugs on BMD is related to reducing vitamin D levels, altering vitamin D metabolism or a direct effect on bone cells, although no definite proof exists for either possibility [26]. In our study there was no clear differential susceptibility of epileptic patients to various AEDs since both hepatic enzyme-inducing and non-inducing AEDs seem to affect BMD in some tested sites. However, the results were not statistically significant due to the small number in each category of various drug combinations. Although many studies suggest that enzyme-inducing AEDs are the only AED type causing severe BMD decline and increased fracture risk [27,28] in epileptic patients this is not always confirmed by other studies. No specific AED type was associated with reduced BMD in a study from England with institutionalized patients [6], whereas there was no evidence that a specific type of AED or vitamin D deficiency were related to bone loss in epileptic patients in a study from Thailand [7] and in a cohort of adult male patients showing bone loss at the hip [29]. Furthermore non-enzyme-inducing antiepileptic drugs were

Table 3 – Mean BMD values in epileptic patients in accordance to AEDs type.

| AED groups | Group A | Group B | Group C | Group D |
|------------------|-------------|-------------|-------------|-------------|
| Patients | N = 10 | N = 7 | N = 16 | N = 5 |
| Lumbar spine BMD | 0.75 ± 0.35 | 0.86 ± 0.16 | 0.97 ± 0.18 | 1.04 ± 0.10 |
| Total hip BMD | 0.93 ± 0.11 | 0.82 ± 0.15 | 0.97 ± 0.15 | 0.91 ± 0.11 |
| Femoral neck BMD | 0.80 ± 0.10 | 0.74 ± 0.19 | 0.84 ± 0.17 | 0.80 ± 0.12 |
| Males | N = 6 | N = 6 | N = 11 | N = 4 |
| Lumbar spine BMD | 0.78 ± 0.34 | 0.91 ± 0.12 | 0.91 ± 0.17 | 1.04 ± 0.11 |
| Total hip BMD | 0.96 ± 0.11 | 0.85 ± 0.14 | 0.95 ± 0.17 | 0.93 ± 0.11 |
| Femoral neck BMD | 0.82 ± 0.12 | 0.78 ± 0.18 | 0.82 ± 0.19 | 0.79 ± 0.14 |

AEDs: antiepileptic drugs; BMD: bone mineral density; Group A: patients on monotherapy or polytherapy of AEDs with either weak or no CYP2C19 inducing or inhibiting properties; Group B: patients on monotherapy or polytherapy of AEDs with CYP2C19 inducing properties; Group C: patients on valproic acid, a CYP2C19 inhibitor, with or without concurrent AEDs with no inducing or inhibiting properties; Group D: patients on a combination of AEDs with enzyme-inducing properties and VPA.

associated with increased rates of bone loss in a recent cross-sectional study, with levetiracetam being the drug more often affecting bone density [30]. In experimental models, new agents, as levetiracetam, have been shown to weaken the femoral neck suggesting a primary effect on bone quality of the newer agents [31].

In the present study, smoking was significantly more common among control individuals compared to epileptic patients (61% versus 36.8%). Smoking is considered a risk factor for low BMD and increased incidence of hip fracture [32], even though the exact mechanism of this association remains obscure but it could be related to the antiestrogenic effect of smoking [33], more noticeable in the elderly [34]. The fact that the epileptic patients in our study were less frequently smokers compared to controls suggests that the actual differences in BMD found in the present study could be even larger. Further prospective studies may clarify these findings with certainty.

5. Conclusion

We acknowledge the small sample size as a major limitation of the present study. Despite that, our findings indicate that epileptic patients, predominantly males, have lower BMD and thus are at risk for osteoporosis, compared to control individuals, independently of the type of the antiepileptic drug use. Larger studies, predominantly prospective randomized, are needed to further establish a role for each antiepileptic drug category on BMD. Screening for BMD with DXA may be considered in epileptic patients regardless of the prescribed AEDs.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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