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Effects of antiepileptic drugs on bone mineral density and bone metabolism in children: a meta-analysis*

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Abstract: Objective: The aim of our meta-analysis was to assess the effects of antiepileptic drugs on bone mineral density and bone metabolism in epileptic children. Methods: Searches of PubMed and Web of Science were undertaken to identify studies evaluating the association between antiepileptic drugs and bone mineral density and bone metabolism. Results: A total of 22 studies with 1492 subjects were included in our research. We identified: (1) a reduction in bone mineral density at lumbar spine (standardized mean difference (SMD)=−0.30, 95% confidence interval (CI) [−0.61, −0.05]), trochanter (mean difference (MD)=−0.07, 95% CI [−0.10, −0.05]), femoral neck (MD=−0.05, 95% CI [−0.09, −0.02]), and total body bone mineral density (MD=−0.33, 95% CI [−0.51, −0.15]); (2) a reduction in 25-hydroxyvitamin D (MD=−3.37, 95% CI [−5.94, −0.80]) and an increase in serum alkaline phosphatase (SMD=0.71, 95% CI [0.38, 1.05]); (3) no significant changes in serum parathyroid hormone, calcium, or phosphorus. Conclusions: Our meta-analysis suggests that treatment with antiepileptic drugs may be associated with decreased bone mineral density in epileptic children.

Key words: Antiepileptic drugs, Bone mineral density, Bone metabolism, Children, Meta-analysis
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1 Introduction

Epilepsy is a common chronic neurological disorder with more than half of cases beginning in childhood (Begley *et al.*, 2000). Most patients require long-term, and sometimes lifelong, therapy with antiepileptic drugs (AEDs). AEDs are associated with significant side effects including, but not limited to, radiological evidence of rickets, decreased bone mineral density (BMD), altered bone turnover, and increased risk of fracture (Souverein *et al.*, 2005; Karceski, 2007; Gniatkowska-Nowakowska, 2010; Verrotti *et al.*, 2010; Meier and Kraenzlin, 2011). AEDs increase catabolism of 25-hydroxyvitamin D by induction of the hepatic P-450 enzyme system, leading to relative hypocalcemia, increased levels of parathyroid hormone (PTH), and subsequent low BMD (Dent *et al.*, 1970; Keck *et al.*, 1982; Chung and Ahn, 1994). However, some studies have suggested a significant reduction in BMD with non-enzyme-inducing AEDs (Oner *et al.*, 2004; Petty *et al.*, 2005). Other environmental and epidemiological parameters including age, sex, diet, and mobility may also affect mineral metabolism (Pack and Morrell, 2001), suggesting a multifactorial etiology.

A meta-analysis, pooling data from multiple cross-sectional studies showed only a very limited decrease in BMD with a decline of 0.4 *Z*-scores in the spine and −0.6 *Z*-scores in the hip (Vestergaard, 2005).

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Most of the relevant data are derived from adults. Data on bone metabolism in children receiving AEDs are scarce, with conflicting results. Some studies found a significant difference in BMD and bone metabolism between children treated with AEDs and healthy controls (Oner *et al.*, 2004; Pack *et al.*, 2008; Salimipour *et al.*, 2013); other studies found no significance (Akin *et al.*, 1998; El-Hajj Fuleihan *et al.*, 2008). However, these studies may be limited, as most included a small sample, and numbers were too few to enable comparison between specific AEDs.

We, therefore, undertook a meta-analysis of studies that had analyzed the effects of AEDs on BMD and bone metabolism in children.

2 Materials and methods

2.1 Search strategy and inclusion criteria

We searched PubMed and Web of Science for all studies up to July 2014 that reported on BMD or bone metabolism and the use of AEDs in children using the keywords "epilepsy" or "antiepileptic drugs" in combination with "bone mineral density" or "bone density" or "bone metabolism" or "bone turnover". This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati *et al.*, 2009). We included studies reporting the effects of AEDs on BMD and bone metabolism in children, regardless of sample size, if they met the following criteria: (1) inclusion of at least one marker of bone metabolism; (2) BMD measured by dual-energy X-ray absorptiometry (DXA); (3) studies involving mean BMD (or bone markers) and standard deviations (SDs) or standard errors (SEs), or where these numbers could be calculated; (4) child subjects (<18 years old); (5) studies assessing patients with epilepsy who received AED monotherapy or polytherapy; (6) studies with a healthy control group; (7) observational studies or randomized controlled trials (RCTs). We excluded animal studies, reviews, and letters.

2.2 Data extraction and quality assessment

Two reviewers independently evaluated studies for inclusion. Discrepancies were resolved by arbitration and consensus following discussion. The following information was extracted from each study: name of the first author, year of publication, country where the study was performed, design of the study, drug dosage, age and gender of individuals, number of cases, mean BMD (or serum concentration of bone markers), and SDs (or SEs). Study quality was independently assessed by two reviewers according to the Newcastle-Ottawa Scale for quality assessment of cohort and case-control studies (Liberati *et al*., 2009). Each study was allocated up to nine stars, the criteria being quality of selection (maximum, 4 stars), comparability (maximum, 2 stars), and outcome (maximum, 3 stars).

2.3 Statistical analysis

When the outcome of interest was measured using the same scale in every study, weighted mean differences (WMDs) with 95% confidence interval (CI) were used as summary measures. However, when studies used different scales to measure the effect of AED treatment, the standardized mean difference (SMD) with 95% CI was used.

All data were initially analyzed by a fixed-effects model if there was no significant heterogeneity, and a random-effects model otherwise. Heterogeneity was assessed by Q statistics, with $P<0.10$ indicating significant heterogeneity. We quantified heterogeneity using the I^2 statistic. I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity, respectively. To explore heterogeneity, we performed subgroup analyses according to the drug patients used.

Publication bias was checked through the use of funnel plots with an asymmetric funnel plot indicating publication bias. All analyses were conducted using Review Manager (RevMan) v.5.2 statistical software and Microsoft Excel. $P<0.05$ was considered statistically significant.

3 Results

3.1 Study selection and characteristics

The information flow for the search and selection of studies is shown in Fig. 1. The initial search yielded 1603 research reports, of which 228 were excluded due to identical title or authors; 1056 were excluded due to ineligible study design (including non-human studies, review articles, case reports,

comment, letter, experimental study, and/or fracture-only outcome). After full-text screening, 22 studies were included (Chung and Ahn, 1994; Baer *et al.*, 1997; Akin *et al.*, 1998; Kafali *et al.*, 1999; Erbayat Altay *et al.*, 2000; Verrotti *et al.*, 2002; Voudris *et al.*, 2002; Ecevit *et al.*, 2004; Oner *et al.*, 2004; Babayigit *et al.*, 2006; Kumandas *et al.*, 2006; Nicolaidou *et al.*, 2006; El-Hajj Fuleihan *et al.*, 2008; Nettekoven *et al.*, 2008; Sheth and Hermann, 2008; Sheth *et al.*, 2008; Gniatkowska-Nowakowska, 2010; Rauchenzauner *et al.*, 2010; Babacan *et al.*, 2012; Dimić *et al.*, 2013; Razazizan *et al.*, 2013; Turan *et al.*, 2014). Table 1 summarizes the characteristics of the included studies published between 1994 and 2014. Nine were conducted in Turkey, six in Europe, one in Australia, one in Korea, one in Iran, one in Lebanon, and three in the United States. Twenty-one studies were written in English, and one in Serbian. Six provided data only on BMD, eight reported results on bone markers, and the remaining eight reported both. Study quality scores (range, 0–9) averaged 7.54, and 63.6% were high-quality studies (score>8) (Table 1).

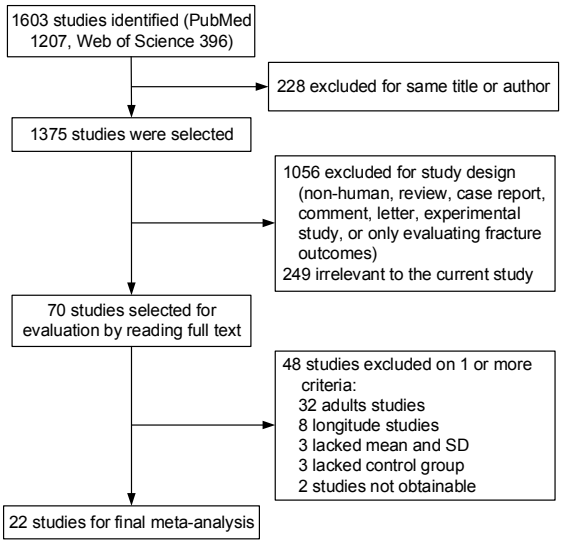

Fig. 1 Flow diagram of the study-selection process

Table 1 Characteristics of the included studies

Study	Country	Design	Outcome	P/V	M/F	Age (year)	Duration (year)	Dose	Quality
Chung and Ahn, 1994	Korea	Retrospective cohort	DEXA lumbar spine	30/PB	48/30	8.5	0.75–8	3–5 mg/(kg·d)	8
				48/PHT					
				78/control		8.5			
Baer *et al.*, 1997	U.S.	Retrospective cohort	Ca	42/AED		5.4			6
				40/control		6.2			
Akin *et al.*, 1998	Turkey	Retrospective cohort	DEXA lumbar spine, calcium, phosphorus, ALP	25/VPA	14/11	8.83	2.4	66 μg/ml	8
				28/CBZ	15/13	9.5	2.6	7.0 μg/ml	
				26/control	15/12	8.92			
Kafali *et al.*, 1999	Turkey	Retrospective cohort	DEXA lumbar spine, Ca, P, ALP	6/CBZ	10/9	M: 8.8	1.7	18.33 mg/(kg·d)	9
				13/VPA		F: 8.4	1.8	18.46 mg/(kg·d)	
				57/control	29/28				
Erbayat Altay *et al.*, 2000	Turkey	Retrospective cohort	DEXA lumbar spine	21/CBZ	5/16	12.81	3.7	10–20 mg/(kg·d)	8
				15/VPA	5/10	10.9	3.1	15–30 mg/(kg·d)	
				22/control	8/14	10.68			
Verrotti *et al.*, 2002	Italy	Prospective cohort	25-hydroxyvitamin D, PTH	60/CBZ	30/30		2	21.9 mg/(kg·d)	7
				60/control	30/30				
Voudris *et al.*, 2002	Greece	Retrospective cohort	ALP	37/CBZ		8.08	>0.5		8
				47/VPA		8.13	>0.5		
				34/PB		2.4	>0.5		
				118/control					
Ecevit *et al.*, 2004	Turkey	Retrospective cohort	DEXA trochanter and femoral neck	17/CBZ	20/13	10.19	2.64	6.26 μg/ml	8
				16/VPA		10.59	2.03	53.75 μg/ml	
				31/control	17/14	11.52			
Oner *et al.*, 2004	Turkey	Retrospective cohort	DEXA lumbar spine, trochanter and femoral neck, Ca, P, ALP	33/VPA	17/16	7.1	1.08	25.6 mg/(kg·d)	8
				33/control	17/16	7.4			

To be continued

Table 1

Study	Country	Design	Outcome	P/V	M/F	Age (year)	Duration (year)	Dose	Quality
Kumandas *et al.*, 2006	Turkey	Retrospective cohort	DEXA lumbar spine, PTH, ALP	33/CBZ	20/13	9.7	2.96	19478.6 mg/kg cumulative dose	8
				33/VPA	17/16	8.8	2.81	22852.4 mg/kg cumulative dose	
				22/control	13/9	8.9			
Nicolaidou *et al.*, 2006	Greece	Prospective cohort	Ca, P, 25-hydroxyvitamin D, PTH	24/CBZ	19/32	7.4	1.93	15–20 mg/(kg·d)	7
				27/VPA				20–25 mg/(kg·d)	
				80/control	38/42	7.6			
Babayigit *et al.*, 2006	Turkey	Retrospective cohort	DEXA lumbar spine, Ca, P, ALP, 25-hydroxyvitamin D	23/CBZ	14/9	12.4	3.65	15–25 mg/(kg·d)	7
				31/VPA	15/16	11.18	3.32	15–40 mg/(kg·d)	
				14/OXC	5/9	13.13	2.36	15–30 mg/(kg·d)	
				30/control	14/16	13.09			
Nettekoven *et al.*, 2008	Germany	Retrospective cohort	Ca, P, 25-hydroxyvitamin D, PTH	38/(CBZ, VPA, etc.)	25/13	8.4	>0.25		8
				44/control	24/20	7.6			
El-Hajj Fuleihan *et al.*, 2008	Lebanon	Retrospective cohort	DEXA lumbar spine, 25-hydroxyvitamin D	88/AED		13.0	4.7		7
				111/control		13.3			
Sheth and Hermann, 2008	U.S.	Cross-sectional	DEXA total body BMD	116/AED		6–18			6
				36/control		6–18			
Sheth *et al.*, 2008	U.S.	Cross-sectional	DEXA total body BMD	18/AED	6/12	11.9	<1		8
				37/AED	19/18	11.8	1–5		
				27/AED	10/17	13.6	>6		
				32/control	13/19	12.8			
Gniatkowska-Nowakowska *et al.*, 2010	Poland	Retrospective cohort	DEXA lumbar spine, Ca, P	126/(CBZ, VPA, LTG, TPM)	80/46	7–16			6
				132/control	87/45	7–16			
Rauchenzauner *et al.*, 2010	Austria	Retrospective cohort	25-hydroxyvitamin D, Ca, P	85/VPA	38/47	12.41	>0.5	869 mg/d	8
				11/LTG	28/12	12.83	>0.5	284 mg/d	
				17/OXC			>0.5	840 mg/d	
				12/SUL			>0.5	150 mg/d	
				41/control	29/12	12.08			
Babacan *et al.*, 2012	Turkey	Retrospective cohort	DEXA lumbar spine, Ca, P, 25-hydroxyvitamin D, PTH	44/OXC	22/22	9.65	1.25		7
				33/control	17/16	10.24			
Dimić *et al.*, 2013	Serbia	Retrospective cohort	DEXA lumbar spine	34/(CBZ, VPA, etc.)	18/16	9.77	M: 2.66 F: 3.33		8
				35/control	16/19				
Razazizan *et al.*, 2013	Iran	Retrospective cohort		48/(CBZ, VPA, PB, TPM)	25/23	7.1	>0.5		8
				48/control	27/21				
Turan *et al.*, 2014	Turkey	Retrospective cohort	25-hydroxyvitamin D	144/(CBZ, VPA, PB)		4–12	>0.5		8
				44/control		8.2			

DEXA, dual-energy X-ray absorptiometry; Ca, calcium; ALP, alkaline phosphatase; P, phosphorus; PHT, phenytoin; PTH, parathormone; BMD, bone mineral density; CBZ, carbamazepine; VPA, valproic acid; OXC, oxcarbazepine; AED, antiepileptic drug; PB, phenobarbital; LTG, lamotrigine; SUL, sulthiame; TPM, topiramate; M, male; F, female; P/V, participants/intervention

3.2 Pooled effect of AED treatment on BMD

A total of 11 studies comprising 23 datasets, which included 645 subjects and 579 controls, evaluated the effect of AEDs on lumbar spine BMD (Chung and Ahn, 1994; Akin *et al.*, 1998; Kafali *et al.*, 1999; Erbayat Altay *et al.*, 2000; Oner *et al.*, 2004; Babayigit *et al.*, 2006; Kumandas *et al.*, 2006; El-Hajj Fuleihan *et al.*, 2008; Gniatkowska-Nowakowska, 2010; Babacan *et al.*, 2012; Dimić *et al.*, 2013). The results suggested an association between AED treatment and decreased BMD (SMD=−0.30, 95% CI [−0.61, 0.01]; Fig. 2), with high heterogeneity (I^2= 85%). When data were pooled for absolute changes in BMD (WMD=−0.03, 95% CI [−0.06, 0.00]) or BMD *Z*-scores (WMD=−0.87, 95% CI [−1.25, −0.48]), decreased BMD was found. No single study influenced the pooled effect significantly. Duration of follow-up and sex ratio did not affect the pooled effect, either. Subgroup analyses showed that the difference in AED type was a source of heterogeneity. As the results suggested, valproic acid (VPA) (SMD=−0.48, 95% CI [−0.95, −0.02]) could significantly decrease BMD of lumbar spine in epileptic children, while carbamazepine (CBZ) (SMD=0.32, 95% CI [−1.08, 1.72]) had no significant effect. The funnel plots indicated no obvious publication bias.

The changes in BMD of trochanter and femoral neck were assessed by three datasets from two studies (Oner *et al.*, 2004; Ecevit *et al.*, 2004) with 66 subjects and 64 controls. The pooled effect showed that AED treatment resulted in a significant decrease of BMD in trochanter (mean difference (MD)=−0.07, 95% CI [−0.10, −0.05]) and femoral neck (MD=−0.05, 95% CI [−0.09, −0.02]) (Table 2). Subgroup analyses revealed that VPA was significantly associated with decreased BMD of trochanter (WMD=−0.08, 95% CI [−0.11, −0.05]) and femoral neck (WMD=−0.07, 95% CI [−0.11, −0.02]). Sensitivity analysis showed that no single study affected the summary estimates significantly. The funnel plots showed no obvious publication bias.

Similarly, meta-analysis of two studies (Sheth and Hermann, 2008; Sheth *et al.*, 2008), which included 198 subjects and 78 controls, and evaluated the effect of AED treatment on total body BMD, obtained a significant result (WMD=−0.33, 95% CI [−0.51, −0.15]). Sensitivity analysis showed that no single study affected the summary estimates significantly. The funnel plots showed no obvious publication bias.

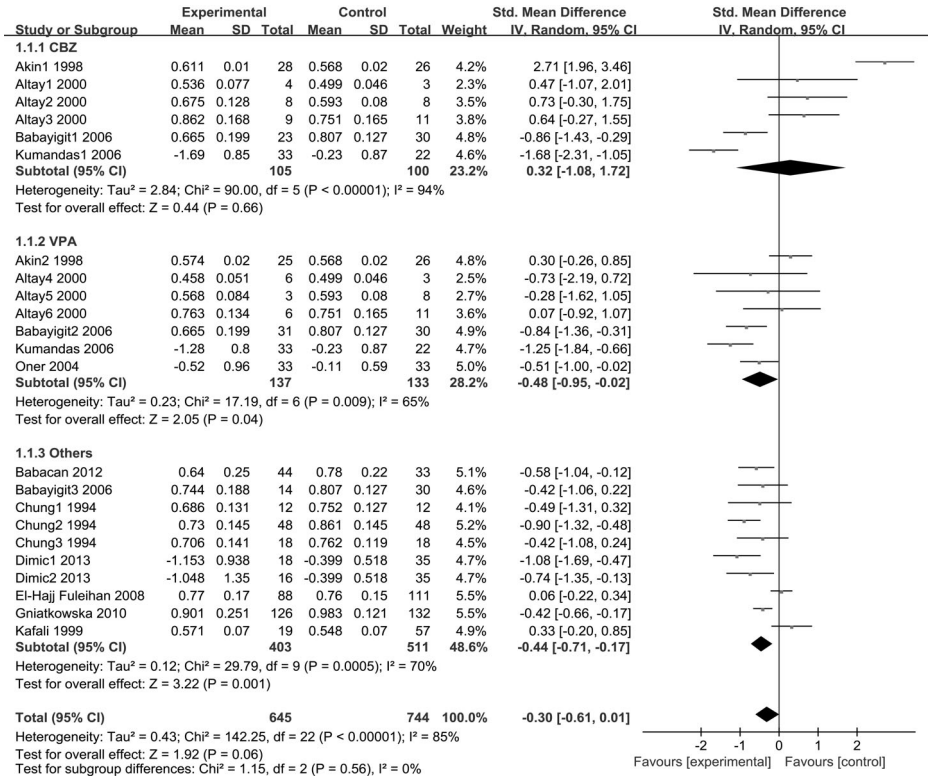

Fig. 2 Meta-analysis of datasets involving AED treatment and BMD of lumbar spine

Table 2 Main analysis for BMD and bone markers

Variable	Dataset/ study	Subject/ control	Summary measure	Estimate (95% CI)	*P*-value	I^2 (%)	Heterogeneity *P*-value
BMD of lumbar spine	23/11	645/579	SMD: −0.30	[−0.61, 0.01]	0.06	85	<0.00001
BMD of trochanter	3/2	66/64	WMD: −0.07	[−0.10, −0.05]	<0.00001	0	0.8
BMD of femoral neck	3/2	66/64	WMD: −0.05	[−0.09, −0.02]	0.002	0	0.54
Total body BMD	5/2	198/78	WMD: −0.33	[−0.51, −0.15]	0.0004	0	0.71
25-Hydroxyvitamin D	16/9	616/421	WMD: −3.37	[−5.94, −0.80]	0.01	84	<0.0001
Alkaline phosphatase	15/8	449/397	SMD: 0.71	[0.38, 1.05]	<0.00001	83	<0.00001
Calcium	17/10	648/570	SMD: −0.49	[−1.03, 0.05]	0.08	95	<0.00001
Phosphorus	13/8	531/441	SMD: −0.16	[−0.70, 0.39]	0.57	94	<0.00001
Parathormone	11/6	287/219	SMD: 0.30	[−0.05, 0.64]	0.05	66	0.002

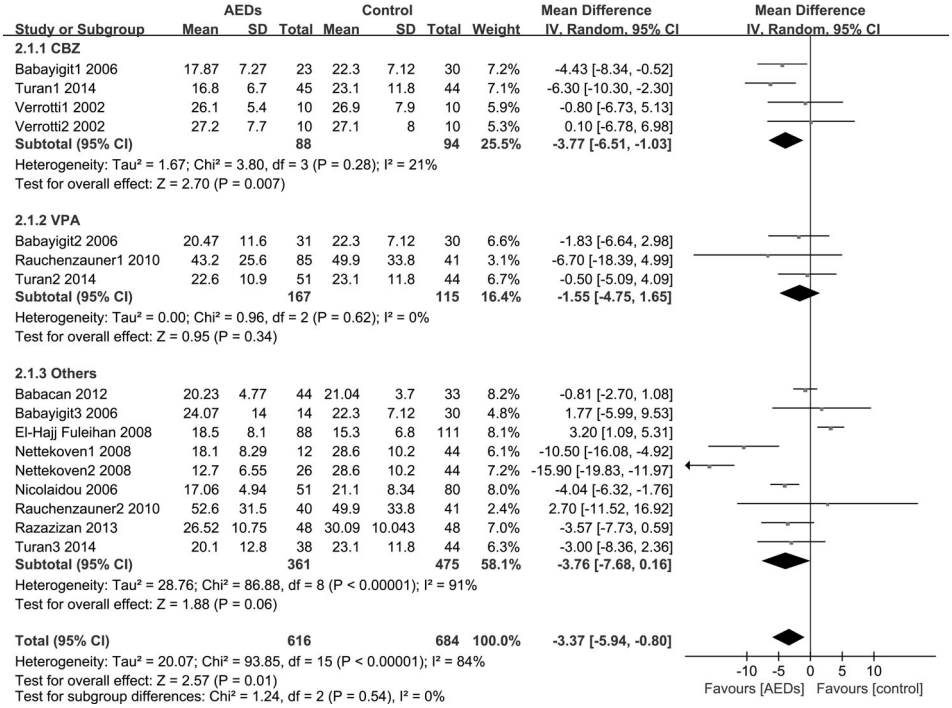

Fig. 3 Meta-analysis of datasets involving AED treatment and 25-hydroxyvitamin D

3.3 Pooled effect of AED treatment on bone markers

The effects of AED treatment on bone markers, including 25-hydroxyvitamin D, serum alkaline phosphatase (ALP), serum calcium, phosphorus, and PTH, were assessed in our study.

Meta-analysis of nine studies including 616 subjects and 421 controls (Verrotti *et al.*, 2002; Babayigit *et al.*, 2006; Nicolaidou *et al.*, 2006; El-Hajj Fuleihan *et al.*, 2008; Nettekoven *et al.*, 2008; Rauchenzauner *et al.*, 2010; Babacan *et al.*, 2012; Razazizan *et al.*, 2013; Turan *et al.*, 2014), revealed a significant association between AED treatment and decreased 25-hydroxyvitamin D (MD=−3.37, 95% CI [−5.94, −0.80]), as shown in Fig. 3. Sensitivity analysis showed that no single study affected the summary estimates significantly. The funnel plots showed no obvious publication bias.

The changes in serum ALP were assessed for 449 subjects and 397 controls from eight studies (Akin *et al.*, 1998; Kafali *et al.*, 1999; Voudris *et al.*, 2002; Oner *et al.*, 2004; Babayigit *et al.*, 2006; Kumandas *et al.*, 2006; Babacan *et al.*, 2012; Razazizan *et al.*, 2013). The pooled effect showed that AED treatment resulted in a significant elevation of serum ALP (SMD=0.71, 95% CI [0.38, 1.05]), as shown in

Fig. 4. Sensitivity analysis showed that no single study affected the summary estimates significantly. The funnel plots showed no obvious publication bias.

No significant effects of AED treatment on serum PTH, serum calcium, or phosphorus were found. The detailed results are shown in Table 2.

4 Discussion

Childhood is a critical time for bone mineralization. During periods of high mineralization, children are prone to osteoporosis and bone fractures (Sheth *et al.*, 1995; Oner *et al.*, 2004). AEDs are one of the most important factors that may affect bone health, but there is no agreement about the effect of AEDs on BMD and bone metabolism of children with epilepsy. Our meta-analysis of studies into the effects of treatment with AEDs on epileptic children shows: (1) a reduction in BMD at lumbar spine, trochanter, femoral neck and total body BMD; (2) a reduction in 25-hydroxyvitamin D and an increase in serum ALP; (3) no significant changes in serum PTH, calcium, or phosphorus.

Although the effect of AED treatment on the lumbar spine BMD was of borderline significance (P=0.06), the omission of studies using BMD Z-scores made the effect significant (P=0.03). The heterogeneity in the analysis was high (I^2=85%). The potentially confounding factors of polytherapy and difference in seizure type may be a source of heterogeneity. El-Hajj Fuleihan *et al*. (2008) demonstrated that polytherapy patients were associated with a significantly lower BMD level than patients treated with monotherapy. Sheth and Hermann (2008) found that children with symptomatic generalized epilepsy appear to be at highest risk for BMD. However, the two factors were not analyzed in this paper because of lack of data, and future studies are warranted to explore this issue further.

CBZ and VPA are the frontline treatments of partial and generalized seizures in children and adults. With conflicting results about the effects of the two drugs on BMD, the mechanism by which AEDs decrease BMD has yet to be fully established. A classical theory holds the view that enzyme-inducing antiepileptic drugs (EIAEDs) decrease BMD by reducing vitamin D levels secondary to the therapeutic

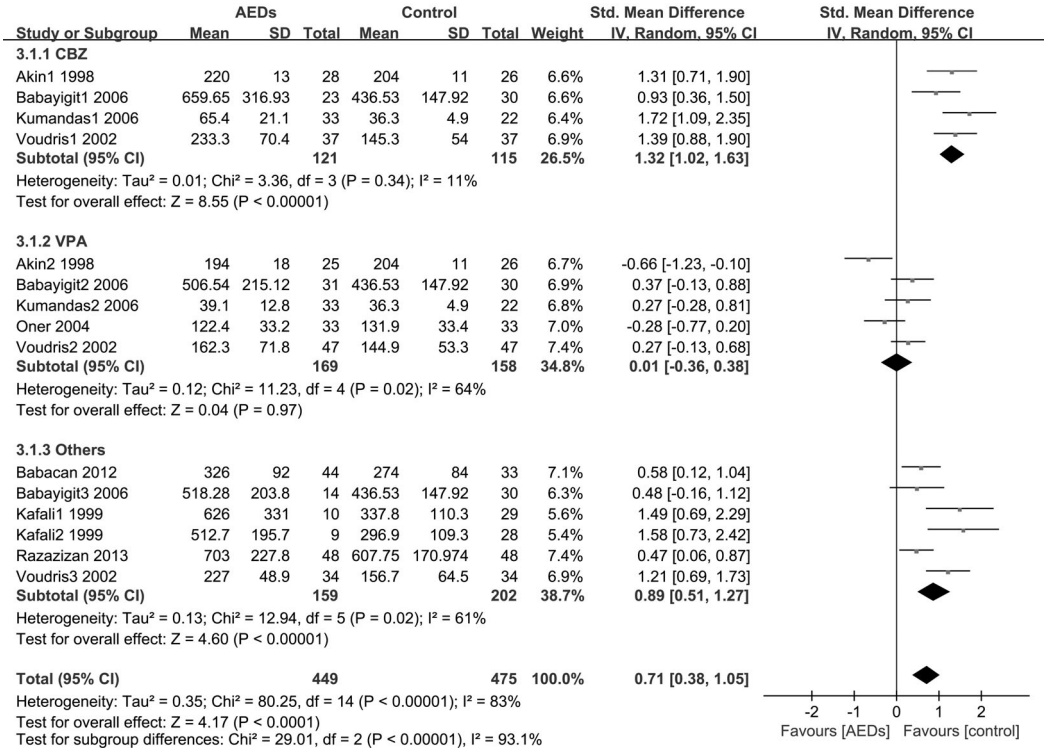

Fig. 4 Meta-analysis of datasets involving AED treatment and BMD of serum ALP

activation of specific cytochrome P450 isoenzymes. Our meta-analysis partially supports this theory by proving that CBZ was associated with lower levels of 25-hydroxyvitamin D (Fig. 3), and no significant difference in BMD among children treated with CBZ compared with controls (Fig. 2). The results also showed that non-EIAEDs, presented as VPA, could result in a significant decrease in BMD. Cerveny *et al*. (2007) suggested that VPA may interfere with bone metabolism by activation of the pregnane X receptor, which promotes the expression of vitamin D-responsive genes. Feldkamp *et al*. (2000) observed a decrease in bone cell proliferation, suggesting that the direct effects of anticonvulsant drugs on bone cells may contribute to skeletal damage. Furthermore, both EIAEDs and non-EIAEDs may also contribute to bone loss by inhibiting intestinal absorption of calcium and activation of vitamin D (Lee *et al.*, 2010).

The newer antiepileptics are believed to have similar efficacy to the older AEDs, but fewer side effects. Babayigit *et al*. (2006) examined CBZ, VPA and oxcarbazepine use in children, and reported no significant differences on lumbar spine BMD between the groups, but 25-hydroxyvitamin D in oxcarbazepine-treated children was significantly higher than that in the VPA group. Rauchenzauner *et al*. (2010) found no significant difference in 25-hydroxyvitamin D between VPA and the newer AEDs. More studies are needed to make direct comparisons between newer and older AEDs in epileptic children.

Low levels of 25-hydroxyvitamin D in AED users have been demonstrated in a number of studies, but not in all. Our results suggest that AEDs affect bone metabolism by reducing 25-hydroxyvitamin D. Low 25-hydroxyvitamin D concentration results in secondary hyperparathyroidism and accelerated bone loss, influencing absorption of calcium and phosphorus (Shellhaas and Joshi, 2010). This theory is consistent with our results. However, no significant changes in serum PTH, Ca, or P were found in our study, suggesting that there are still gaps in our knowledge of the impact of AEDs on bone metabolism.

Total ALP is considered a reliable biochemical marker of bone formation. The present meta-analysis demonstrates that children treated with AEDs have a significantly increased ALP level. However, the pooled results suggest that increased serum ALP is significantly associated with the use of CBZ and the newer antiepileptics, but not VPA, indicating that ALP is an inadequate marker for bone metabolism. It could be hypothesized that measurement of total ALP may simply reflect hepatic metabolism. Some studies consider ALP isoenzyme to be highly sensitive and specific to increased bone metabolism (Voudris *et al.*, 2002; 2005). A longitudinal study showed that epileptic patients using CBZ can have their bone metabolism altered early in the course of treatment, as indicated by the elevated activity of serum bone ALP isoenzyme (Voudris *et al.*, 2005). Voudris *et al*. (2002) reported that elevated bone ALP isoenzyme correlates with the duration of treatment in children on VPA without a concomitant significant elevation of total ALP. Bone ALP isoenzyme, but not total ALP, may therefore be used as a marker for the selection of patients who might benefit from a comprehensive evaluation of their bone metabolism profile.

There is no agreement about the relationship between BMD and vitamin D status. Hannan *et al*. (2008) showed that serum 25-hydroxyvitamin D and BMD were significantly related to one another in white men only. Mikati *et al*. (2006) conducted the only randomized, controlled trial that demonstrated no significant difference between high- and low-dose vitamin D treatments, and no change in BMD compared with healthy controls after one year of treatment. Although there is no consensus on optimal vitamin D levels, many physicians often rely on 25-hydroxyvitamin D levels to evaluate bone health. However, a recent meta-analysis based on a large population indicated that vitamin D given alone was not effective in preventing fractures (Reid *et al.*, 2014). The meta-analysis performed by Vestergaard (2005) showed that the BMD decrease in AED users was in a range consistent with the increase in fracture risk observed, if seizure-related fractures were excluded. The risk of fractures was only slightly higher compared with the general population (risk ratio (RR)=1.3, 95% CI [1.0–1.7]). Since many studies have confirmed the value of BMD for predicting fracture risk, BMD measurement may be an adequate surrogate for bone health. However, we suggest that BMD should be reserved for those with exceptionally high risk (e.g. history of fractures).

Ambulatory status can affect markers of bone metabolism and BMD. Baer *et al*. (1997) studied vitamin D levels in relation to ambulatory status in a

large sample of children who lived at home. They found that the risk of vitamin deficiency among nonambulatory children was about twice that of ambulatory children (χ^2=20.9; P<0.001). They concluded that ambulatory status correlates with abnormalities in the status of 25-hydroxyvitamin D, calcium, and bone. Another study reported no association between ambulatory status and 25-hydroxyvitamin D levels (Bergqvist *et al.*, 2007).

There were limitations to this meta-analysis. One is that the studies included were limited to cohort studies. There have been no RCTs comparing BMD and/or bone metabolism in children treated with AEDs and healthy controls. Studies to date are of limited quality. Duration of follow-up, sex ratio, and dose of drug are not clear in some studies, making it difficult to do sensitive analysis. Important confounders, such as nutrition and season, were not always fully controlled for, which might have resulted in some over-estimation of effects due to residual confounding. The studies are grouped without adequate separation of drugs by metabolic pathway for lack of BMD or bone turnover markers corresponding to the drug used. Besides, most studies lump together a variety of drugs, some of them in monotherapy and some in polytherapy: data on specific drugs are needed. Most of the studies have used a small sample, making it difficult to compare the effects of specific AEDs. Eligible studies came from a limited number of countries, nine of 14 studies targeting BMD coming from Turkey. Duration of treatment and dose also differed widely among studies.

5 Conclusions

Findings from our meta-analysis indicate that AED treatment is associated with decreased BMD in epileptic children. BMD monitoring should be reserved for epileptic children with exceptionally high risk for abnormal bone health. In the absence of evidence to the contrary, it seems reasonable to offer supplements and optimize 25-hydroxyvitamin D levels. Further research is needed to clarify the particular subgroups, dosages, and other factors that may influence the effects of AEDs on BMD and bone metabolism.

Compliance with ethics guidelines

Ying ZHANG, Yu-xin ZHENG, Jun-ming ZHU, Jian-min ZHANG, and Zhe ZHENG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：抗癫痫药物影响儿童骨矿物质密度及骨代谢的荟萃分析

目　的：癫痫是神经系统常见病，半数以上患者儿童时期便发病，癫痫病患者常需终身服用抗癫痫药。研究表明，长期服用抗癫痫药物会影响骨代谢，加速骨矿物质的丢失，导致骨质疏松。但是，每种抗癫痫药物的具体作用还不清楚。作为典型的肝酶诱导剂的抗癫痫药物，卡马西平已经公认有降低骨密度的作用，但是作为非肝酶诱导剂的丙戊酸钠，还没有定论。在新型抗癫痫药物中，奥卡西平、托吡酯和拉莫三嗪等对骨密度似乎没有影响，但目前相关的研究很少，各研究所得结果也不一致。本研究拟通过荟萃分析评估抗癫痫药对癫痫病儿童骨密度和骨代谢的影响。

创新点：目前已有荟萃分析评估抗癫痫药对成人骨密度的影响，但尚无研究分析抗癫痫药对儿童的影响。

方　法：检索 PubMed 和 Web of Science 数据库中评估抗癫痫药与儿童骨密度及骨代谢关系的临床试验。入选标准为：（1）至少包括一项骨代谢的标志物；（2）骨密度用双能×线吸收计量法计算；（3）研究结果包括平均的骨密度和骨密度的标准差；（4）年龄小于 18 岁；（5）患者采用单药或多药治疗；（6）具有健康对照组；（7）必须是观察性研究或随机对照研究。采用固定效应模型和随机效应模型对 22 篇文献的 1492 例患者中的骨密度及骨代谢资料进行荟萃分析，结果用加权均数差（WMD）或标准均数差（SMD）进行评估。

结　论：共 22 篇文献符合纳入标准，共计 1492 例患者。荟萃分析的结果显示，抗癫痫药物的使用可以引起儿童：（1）腰椎、转子、股骨颈的骨密度和全身骨密度的下降；（2）维生素 D 下降和血清碱性磷酸酶的上升；（3）甲状旁腺激素、钙和磷没有显著改变。荟萃分析的结果表明，抗癫痫药的使用可能和癫痫病患儿骨密度降低相关。

关键词：抗癫痫药；骨密度；骨代谢；荟萃分析