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Review

Effects of valproic acid on bone mineral density and bone metabolism: A meta-analysis

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ABSTRACT

Purpose: Numerous studies have shown that the risk of fracture is increased by long-term antiepileptic drugs (AEDs). Valproic acid (VPA) is one of the most commonly used AEDs. In this meta-analysis, we aimed to assess the effects of VPA on bone mineral density (BMD) and bone metabolism.

Methods: PubMed, Embase, Cochrane and Web of Science databases were searched from inception to January 2019 for articles focusing on the effects of VPA on BMD and bone metabolism in adults or children. A meta-analysis was performed using RevMan 5. 3 software.

Results: 18 studies were included in the meta-analysis. The BMD of lumber spine (MD = −0.06, 95%CI: −0.09 to −0.03, P < 0.0001) and femoral neck (MD = −0.05, 95% CI = −0.08 to −0.01, P = 0.02) was markedly decreased in the VPA group compared to healthy controls. Serum bone-specific alkaline phosphatase (BALP) level (SMD = 0.85, 95% CI: 0.30–1.40, P = 0.002) was notably increased in the VPA group compared to healthy groups. In the child group, the serum parathyroid hormone (PTH) level was higher than in healthy groups (SMD = -0.22, 95% CI: −0.40 to −0.04, P = 0.02); besides, the serum 25-hydroxy vitamin D3 (25(OH)D3) level was decreased (SMD = -0.22, 95% CI: −0.40 to −0.04, P = 0.02), while no significant alteration of these parameters was noted in the adult VPA group (P ≥ 0.05).

Conclusions: VPA may reduce the BMD of lumbar spine and femoral neck in patients with epilepsy while increasing the serum BALP level. Serum PTH level are increased and serum 25(OH)D3 level decreased in children with epilepsy treated with VPA. These parameters were unaltered in adults.

1. Introduction

Epilepsy is a neurological disease, influencing about 65 million individuals worldwide [1]. It has been reported that patients with epilepsy typically experience clinical problems in their bones [2]. This disease may associate with multiple factors, such as long-term use of antiepileptic drugs(AEDs), coexisting cerebral palsy and mental retardation, reduced physical activity, inappropriate dietary habits with insufficient vitamin D intake, and reduced exposure to sunlight [3]. A strong evidence indicated an association between AEDs and bone abnormalities, ranging from disorders of bone mineral metabolism to decrease in bone mineral density (BMD) to increase fracture risk [4]. In addition, it has been expressed that more than 50% of patients with epilepsy who take AEDs suffer from bone abnormalities [5].

Typical enzyme-inducing antiepileptic drugs (EIAEDs), such as phenytoin, carbamazepine, and phenobarbital have been reported to reduce BMD and affect bone metabolism. There was no agreement regarding the effects of valproic acid (VPA) as enzyme inhibitor on BMD and bone metabolism [6]. A number of studies [7–10] found that chronic VPA therapy for more than 1 year was associated with decreased BMD in patients with epilepsy, while others [11–14] demonstrated that VPA monotherapy did not increase bone loss. Therefore, the present meta-analysis was conducted to assess the effects of VPA on BMD and bone metabolism markers in patients with epilepsy.

2. Methods

We conducted a meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This meta-analysis was certified according to the

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Box 1
Illustration of the process of literature searching in PubMed database.

#1 "Epilepsy"[Mesh]
#2 'Seizure Disorder'[Title/Abstract]
#3 'Seizures, Epileptic'[Title/Abstract]
#4 'Epilepsy, Cryptogenic'[Title/Abstract]
#5 Aura[Title/Abstract]
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 "Valproic Acid"[Mesh]
#8 'Propylisopropylacetic Acid'[Title/Abstract]
#9 Divalproex[Title/Abstract]
#10 Depakene[Title/Abstract]
#11 #7 OR #8 OR #9 OR #10
#12 "Bone Density"[Mesh]
#13 'bone mineral density'[Title/Abstract]
#14 'bone mineral content'[Title/Abstract]
#15 #12 OR #13 OR #14
#16 'bone metabolism'[Title/Abstract]
#17 "Osteoporosis"[Mesh]
#18 osteoporoses[Title/Abstract]
#19 #17 OR #18
#20 #15 OR #16 OR #19
#21 #6 AND #11 AND #20

International Prospective Register of Systematic Reviews (PROSPERO) on 29 January 2019 (Registration No. CRD42019123650).

2.1. Search strategy

Two researchers (DY.F. and J.M.) respectively searched in the PubMed, Embase, Cochrane and Web of Science databases to find out articles written in English related to the effects of VPA on the BMD and bone metabolism from inception to January 2019. The search terms were as follows: “Epilepsy” [Mesh], “Seizures, Epileptic”, “Seizure Disorder”, “Valproic Acid” [Mesh], “Divalproex”, ‘Depakene”, “Propylisopropylacetic Acid”, “Bone metabolism”, “Bone Density” [Mesh], “Bone mineral density”, “Bone mineral content”, “Osteoporosis” [Mesh], and “Osteoporoses”. Taking PubMed database as an example, the process of literature searching is shown in Box 1.

2.2. Study selection, data extraction and quality assessment

The following inclusion criteria were applied:1) study focusing on the effects of VPA on BMD and bone metabolism in patients with epilepsy, in which all the patients received no additional medication, vitamin or supplements, and none of the patients had motor and mental retardation, cerebral palsy, abnormal neurological examination findings or brain injury, 2) the study was designed as a cohort study and a cross-sectional study, 3) enrollment of healthy controls, 4) measuring of the serum levels of 25-hydroxyvitamin D [25(OH)D_3], calcium(Ca), parathyroid hormone (PTH), and bone-specific alkaline phosphatase (BALP), 5) measuring of BMD in lumber spine, femoral neck, and total hip, 6) calculation of mean and standard deviation (mean ± SD) of BMD (or bone metabolism).

The titles and abstracts of the identified articles were checked and independently reviewed by two of the authors (DY.F. and J.M.), and any discrepancies was resolved by discussion or consulting with the senior author (MZ.S.). The data extraction included the following items: basic information (the first author, publication year, study location, study design); baseline characteristics of the study subjects (gender, age, sample size of test group and control group, duration of drug therapy, etc.); Outcome indicators (BMD of lumber spine, femoral neck, and total hip, bone metabolism markers of serum 25(OH)D_3, Ca, PTH, and BALP).

The two authors separately assessed the quality of the included studies. Any disagreement was resolved via discussion with a third reviewer, after which the study was re-evaluated. We evaluated cohort studies using the Newcastle Ottawa Scale(NOS) in the domains of selection, comparability, and outcome. And we assessed cross-sectional studies according to a checklist presented by the Agency for Healthcare Research and Quality (AHRQ). The AHRQ checklist consists of 11 items, with categories of ‘yes’, ‘no’, or “unclear’.

2.3. Statistical analysis

All statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration). The BMD was measured using the same scale in each study, thus, mean difference (MD) with 95% confidence interval (95%CI) were used to compare continuous variables. The bone metabolism was measured using different scales in each study, therefore, the standardized mean difference (SMD) and the 95%CI were employed. The I^2 was used to examine between-study heterogeneity. If $I^2 > 50\%$, the heterogeneity was unacceptable. The data were analyzed by using a random-effects model. If $I^2 < 50\%$, the heterogeneity was acceptable and the data were analyzed with a fixed-effects model. Statistical significance was set at $P < 0.05$.An obvious heterogeneity was treated by subgroup analysis or sensitivity analysis, or only descriptive analysis.

3. Results

3.1. Study identification and selection

A flow diagram of the identification of studies was shown in Fig. 1. Among a total of 513 studies that were identified from the initial search. After removing duplication, 461 articles remained. After the abstracts and titles of 388 studies were reviewed, 73 articles remained. Through the full text review, 73 studies were excluded. Finally, 18 articles met our inclusion criteria, and these were included in this meta-analysis (Table 1).

3.2. Quality assessment of included studies

Results of quality assessments of the final 18 studies are presented in Tables 2 and 3.

3.3. Meta-analysis of BMD of lumbar spine

Nine studies reported the data related to the effects of VPA on BMD

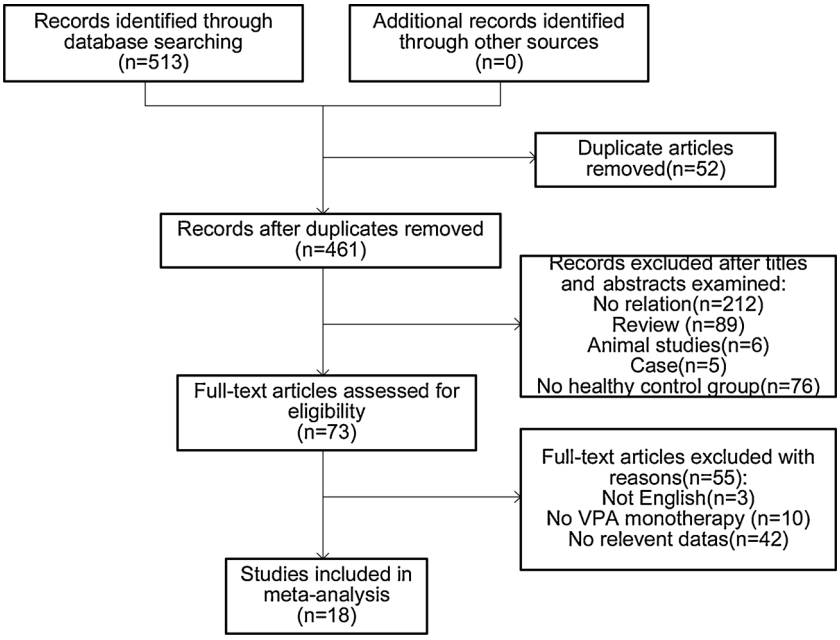

Fig. 1. Flow diagram of the literature search and study selection process.

of lumbar spine. The random-effects model showed that BMD of lumbar spine in the VPA group was significantly lower than that in the control group (MD = −0.06, 95%CI: −0.09 to −0.03, P < 0.0001). Subgroup analysis was performed according to the patients' age (children: < 18 years old). The BMD of lumbar spine in child VPA group (MD = −0.05, 95%CI: −0.08 to −0.01, P = 0.008) and adult VPA group (MD = −0.07, 95%CI: −0.12 to −0.02, P = 0.006) was remarkably lower than that in the control group (Fig. 2).

3.4. Meta-analysis of BMD of femoral neck

Six studies were included in the meta-analysis of BMD of femoral neck. The random-effects model revealed that the BMD of femoral neck in the VPA group was lower than that in the control group (MD = -0.05, 95% CI: -0.08 to -0.01, P = 0.02). Subgroup analysis was undertaken according to the patients' age. The BMD of femoral neck in the adult VPA group was lower than that in the control group (MD = −0.05, 95% CI: −0.10 to −0.00, P = 0.03). There was no significant difference regarding the effects of VPA on BMD of femoral neck between the child VPA group and the control group (MD = −0.02, 95% CI: −0.10 to 0.05, P = 0.53) (Fig. 3).

Table 2
Quality of the cohort studies according to the NOS.

Study	Selection	Comparability	Outcome	Total score
Hasaneen et al. [10]	★★★★	★★★	★★	9
Shiek et al. [15]	★★★☆	★★★	★★	8
Verrotti et al. [20]	★★★★	★★★	★★	9
Boluk et al. [9]	★★★★	★★★	★☆	8

★, present and with score = 1; ☆, not without presentation or being unclear and with score = 0.

Table 1
Characteristics of the studies included in the meta-analysis.

Study	Country	Design	Outcome	VPA		Control		Duration (year)
				P(M/F)	Age(year)	C(M/F)	Age(year)	
Hasaneen et al. [10]	Egypt	Co	①④⑤	21(13/8)	6.2 ± 3.1	80 (41/39)	8.7 ± 3.4	1.45
Shiek et al. [15]	Australia	Co	①②③	13(7/6)	43 ± 18	53(33/20)	44 ± 15	1
Albaghdadi et al. [7]	Iraq	Cr	①②③④⑤⑥	50(18/32)	27.2 ± 5.1	50 (17/33)	26 ± 7.2	8.4 ± 5.3
Serin et al. [12]	Turkey	Cr	②④⑤⑥	28 (17/11)	8.11 ± 3.95	20(7/13)	7.6 ± 3.3	≥2
Turan et al. [16]	Turkey	Cr	⑥	51(-)	4-12	44(-)	8 .2	≥0.5
Salimipour et al. [6]	Iran	Cr	①②③	22(-)	21.8 ± 10.31	38(-)	30 ± 6.13	3.60
Zare et al. [17]	Iran	Cr	④⑤⑦	62(14/48)	25.6 ± 0.9	40(8/32)	23.3 ± 0.8	8.5 ± 1.1
Heo et al. [18]	Korea	Cr	④⑤⑥⑦	32(0/32)	28.5 ± 6.8	36(0/36)	28.4 ± 6.5	6.6
Aksoy et al. [19]	Turkey	Cr	①④⑤⑥	53(25/28)	8.4 ± 2.0	50(31/19)	8.2 ± 1.9	≥2
Verrotti et al. [20]	Ttaly	Co	④⑤⑥⑦	20(-)	≥18	20(-)	–	1
Kwasa et al. [11]	Kenya	Cr	④	57(0/57)	26.4 ± 7.7	53(0/53)	28.7 ± 9.3	≥1
Rauchenzauner et al. [21]	Australia	Cr	⑤⑥	85(38/47)	12.4	41(29/12)	12.1	≥0.5
Babayigit et al. [22]	Turkey	Cr	①④⑤⑥	31(15/16)	11.18 ± 4.07	30(15/15)	13.09 ± 3.09	3.32 ± 1.09
Kumandas et al. [23]	Turkey	Cr	①④⑤	33(16/17)	8.8 ± 2.0	22(9/13)	8.9 ± 2.3	≥2
Oner et al. [24]	Turkey	Cr	①④	33(-)	7.1 ± 3.5	33(-)	7.4 ± 2.8	≥0.5
Ecevit et al. [25]	Turkey	Cr	②	16(-)	10.59 ± 3.16	31(-)	11.52 ± 2.61	2.03 ± 0.88
Boluk et al. [9]	Turkey	Co	①②④⑤	50(24/26)	28.9 ± 5.0	60(30/30)	30.4 ± 5.6	6.7 ± 4.0
Voudris et al. [26]	Greece	Cr	⑦	47(-)	8.1 ± 3.9	47(-)	8.1 ± 3.9	1-5

Co = cohort study, Cr = Cross-sectional study, ①BMD of lumber spine, ②BMD of femoral neck, ③BMD of total hip, ④ serum calcium, ⑤serum PTH, ⑥serum 25(OH)D_3, ⑦serum BALP, P: patients with epilepsy, C: control, M/F: Male/Female, -: Not reported.

Table 3
Quality of the cross-sectional studies according to the AHRQ.

Study	Quality assessment by AHRQ											
	1	2	3	4	5	6	7	8	9	10	11	Score
Albaghdadi et al. [7]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Serin et al. [12]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Turan et al. [16]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Salimipour et al. [6]	★	★	★	☆	☆	☆	★	★	☆	★	☆	6
Zare et al. [17]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Heo et al. [18]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Aksoy et al. 19]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Kwasa et al. [11]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Rauchenzauner et al. [21]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Babayigit et al. [22]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Kumandas et al. [23]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Oner et al. [24]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Ecevit et al. [25]	★	★	★	☆	☆	★	★	★	☆	★	☆	7
Voudris et al. [26]	★	★	★	☆	☆	★	★	★	☆	★	☆	7

1.Source of information; 2. Inclusion and exclusion criteria; 3. Period; 4. Consecutive subjects; 5. Subjective components; 6. Quality assurance; 7. Explanation of exclusions; 8. Control of confounding factors; 9. Handling of missed data; 10. Completeness of data collection; 11. Follow-up. ★, Present with score = 1; ☆, Absence or unclear with score = 0.a

3.5. Meta-analysis of BMD of total hip

Four studies reported the data related to the effects of VPA on BMD of total hip. All patients in the VPA group were adult. The fixed-effects model uncovered that there was no significant difference in BMD of total hip between the VPA group and the control group (MD = −0.01, 95% CI: −0.04 to 0.03, P = 0.77) (Fig. 4).

3.6. Meta-analysis of serum calcium level

A total of 13 articles expressed the data related to the effects of VPA on serum calcium level. The random- effects model disclosed there was no significant difference regarding the effects of VPA on serum calcium level between the VPA group and the control group (SMD = 0.01, 95% CI: −0.50 to 0.51, P = 0.98). Subgroup analysis was performed according to the patients' age. Compared with control group, there was no significant difference in the child VPA group (SMD = 0 .04, 95% CI: −0.61 to 0.70, P = 0.90) or the adult VPA group (SMD = −0.04, 95% CI: −0.88 to 0.81, P = 0.93) (Fig. 5).

3.7. Meta-analysis of serum PTH level

Nine studies were included in the meta-analysis of serum PTH level. The random-effects model disclosed that there was no significant difference regarding the effects of VPA on serum PTH level between the VPA group and the control group (SMD = 0.30, 95% CI: 0.11 to 0.50, P = 0.002). Subgroup analysis was undertaken according to the patients' age. It was noted that serum PTH level in child VPA group was higher than that in the control group (SMD = 0.42, 95% CI: 0.16 to 0.68, P = 0.002). There was no significant difference between the adult group and the control group (SMD = 0.23, 95% CI: -0.08 to 0.54, P = 0.14) (Fig. 6).

3.8. Meta-analysis of serum 25(OH)D3 level

Nine studies reported the data related to the effects of VPA on serum 25(OH)D_3 level. The fixed-effects model showed that the serum 25(OH)D_3 level in the VPA group was lower than that in the control group (SMD = -0.18, 95% CI: -0.33 to -0.03, P = 0.02). Subgroup analysis was performed according to the patients' age. Additionally, serum 25(OH)D_3 level in the child VPA group was lower than in the control group (SMD = -0.22, 95% CI: -0.40 to -0.04, P = 0.02); there was no significant difference in serum 25(OH)D_3 level between the adult VPA group and the control group (SMD = -0.08, 95% CI: -0.35 to 0.19, P = 0.56) (Fig. 7).

3.9. Meta-analysis of serum BALP level

Four studies reported the data related to the effects of VPA on serum BALP level. There was one study showed that the serum BALP level in the child VPA group was higher than that in the control group (SMD = 0.90, 95% CI: 0.47–1.32). The random-effects model of the other three studies revealed that serum BALP level in the adult VPA group was significantly higher than that in the control group (SMD = 0.85, 95% CI: 0.30–1.40, P = 0.002) (Fig. 8).

3.10. Sensitivity analysis

Excluding ineligible studies one-by-one and re-conducting the meta-analysis did not significantly influence the outcomes, indicating that the results of the present meta-analysis were promising.

3.11. Publication bias

In the current study, 13/18 articles concentrated on the influences of VPA on serum calcium level were involved. Therefore, the funnel

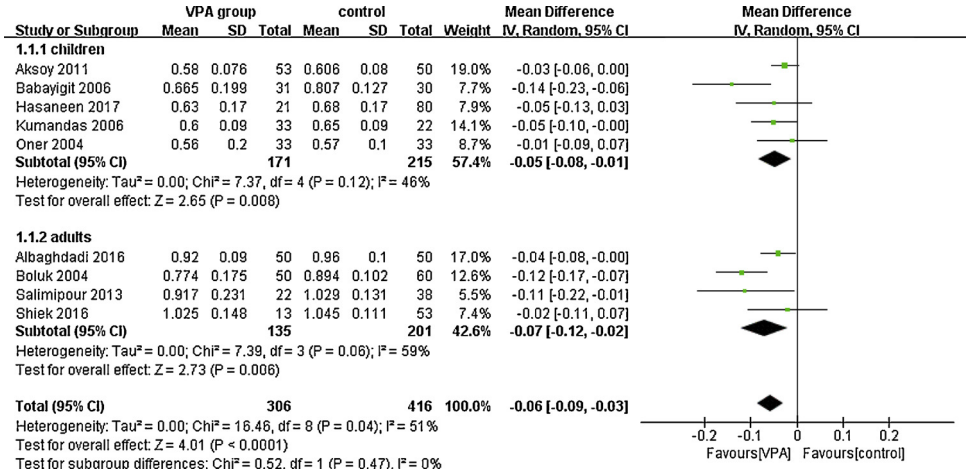

Fig. 2. Meta-analysis of the effects of VPA on BMD of lumbar spine.

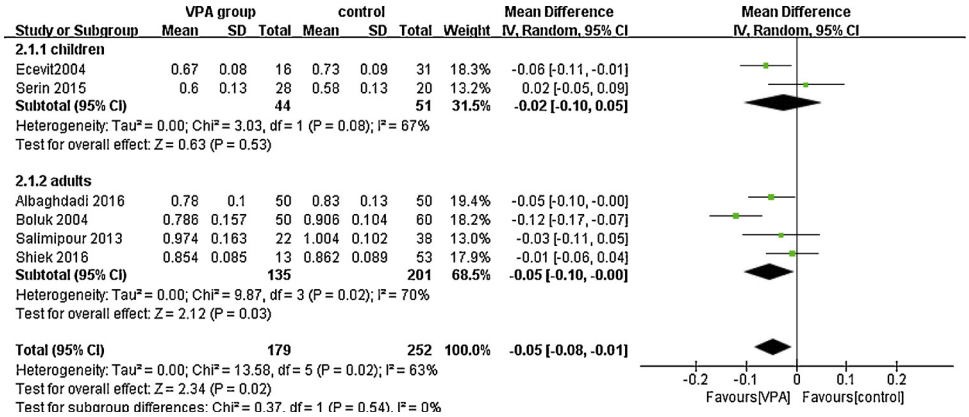

Fig. 3. Meta-analysis of the effects of VPA on BMD of femoral neck.

plot was used to detect bias in studies included in the meta-analysis (Fig. 9). The results showed that there was no publication bias.

4. Discussion

A total of 18 studies were eventually included in our meta-analysis. Besides, the following significant results were achieved: (1) BMD of lumbar spine and femoral neck were notably decreased in patients with epilepsy; (2) Serum BALP level was remarkably increased in patients with epilepsy; (3) Serum PTH level was increased and the serum 25(OH)D_3 level was decreased in child patients with epilepsy, while no significant change in adults was observed.

The mechanisms of AEDs, influencing bone metabolism are multifactorial, including activation of cytochrome P450 enzymes, increase of bone turnover, increase of loss of urinary calcium and urinary phosphorus, etc. [27]. Vitamin D3 plays a substantial role in maintaining the balance between serum phosphorus and calcium. The induction of p450 enzymes by EIAEDs, such as carbamazepine and phenytoin may reduce activity of 1,25(OH)2D by enhancing its degradation and converting 25OHD to inactive metabolites [28,29]. The decreased activity of Vitamin D leads to attenuated absorption of calcium in the intestine, resulting in hypocalcemia and an increase in circulating PTH [30]. Hyperparathyroidism leads to increased bone resorption, and ultimately reduced BMD and increased fracture risk [31]. VPA is the most widely used drug of AED, a liver enzyme inhibitor, however, its influences on BMD and bone metabolism remained controversial. It is thought to work by stimulating osteoclast activity, which may lead to an imbalance between bone formation and resorption, leading to bone loss [19].

The results of the present meta-analysis showed that VPA can reduce the BMD of the lumbar spine and femur neck, and has no significant influence on BMD of the total hip. It is likely because total hip is mainly composed of cortical bone, and the metabolic conversion rate is lower than that in the lumbar spine and femur neck [32].

A reduction in serum 25(OH)D_3 level was found in VPA group. The serum 25(OH)D_3 level was decreased in children with epilepsy, while no significant change was noted in adults. Moreover, serum PTH level was increased in children with epilepsy, while no notable change was observed in adults. Childhood and adolescence are the most critical periods in skeletal development [19]. As children are still in the growth period and regulation of their bone metabolism regulation system may not be comparable with adults, thus, serum levels of 25(OH)D_3 and PTH in children are more susceptible. Meier et al. found that coexisting effect of limited movement or gait may result in impaired bone mass in children and adolescents [33]. But May et al. reported that age and height had no remarkable influence on the VPA concentration [34]. A study showed that without-enzyme inducing comedication, clearance rates of VPA in the elderly were comparable to those observed in the young controls [35]. A lot of research is still needed to find the difference.

Furthermore, VPA has no significant influence on serum calcium level. Serum calcium level is affected by hormones, such as PTH and 25(OH)D_3, thus, the change of serum calcium level is not as sensitive as PTH and 25(OH)D_3. A previous research demonstrated that patients with osteoporosis have normal serum calcium level before treatment [36].

The present meta-analysis contains a number of limitations. First, the included studies were observational studies, hence, the bias of selection and implementation could not be avoided. Second, several important factors, such as diet, sunlight exposure and exercise were not mentioned in the included studies.

5. Conclusion

In summary, VPA may reduce the BMD of lumbar spine and femoral neck in patients with epilepsy while increasing the serum BALP level. Serum PTH level are increased and serum 25(OH)D3 level decreased in children with epilepsy treated with VPA. These parameters were unaltered in adults. Therefore, BMD of lumbar spine, and femoral neck, as well as bone mineral markers, such as serum levels of 25 (OH) D_3, PTH, and BALP should be regularly examined in patients taking VPA for long-time treatment, especially in children.

Authors' contributions

Danyang Fan, was in charge of searching process, study design, quality assessment, data collection, data analysis, and drafting the manuscript. Jie Miao was responsible for searching process, study

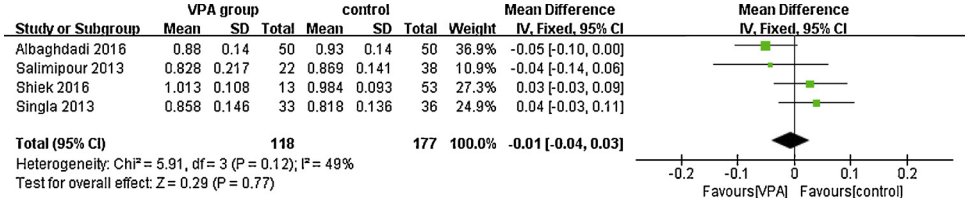

Fig. 4. Meta-analysis of the effects of VPA on BMD of total hip.

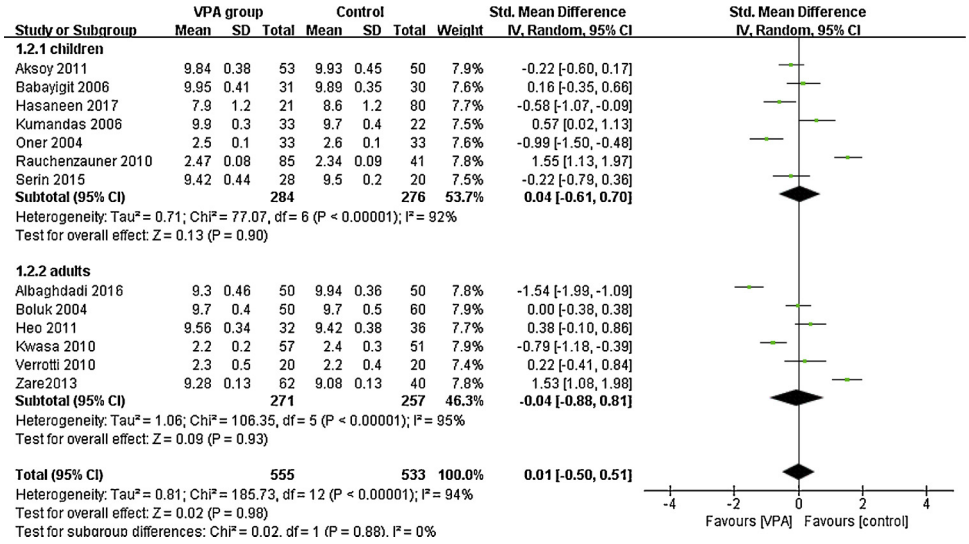

Fig. 5. Meta-analysis of the effects of VPA on serum calcium level.

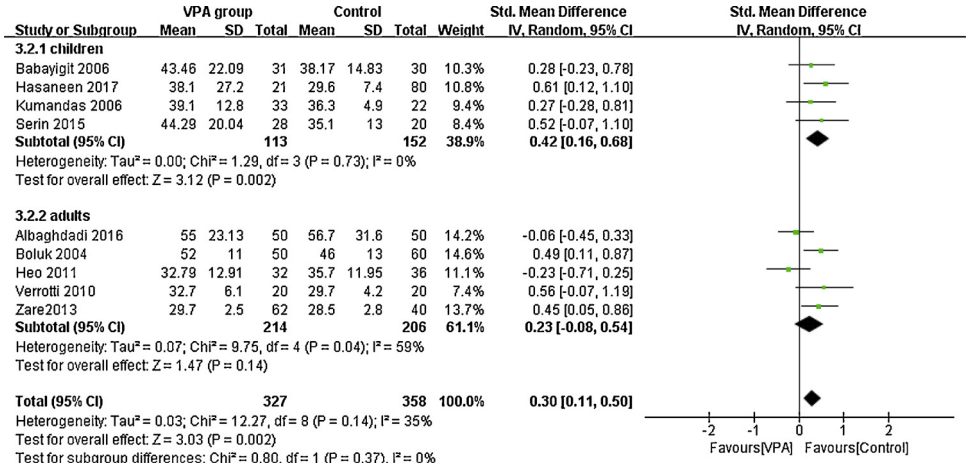

Fig. 6. Meta-analysis of the effects of VPA on serum PTH level.

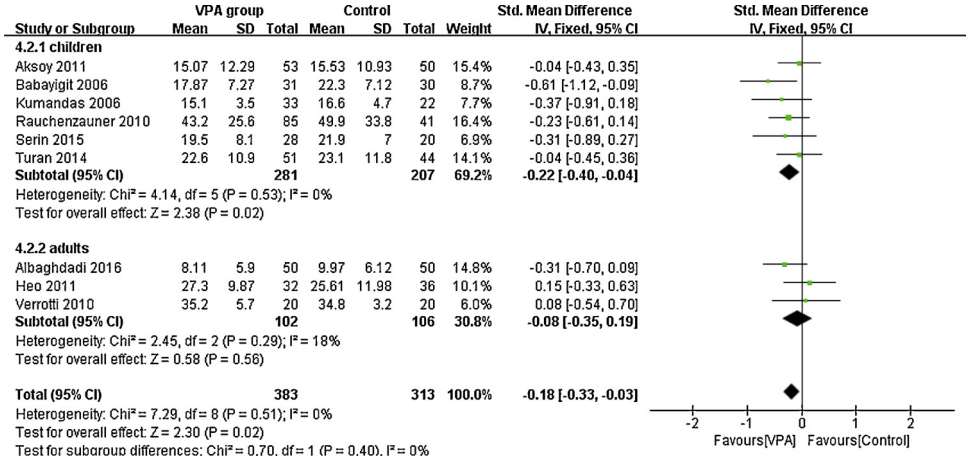

Fig. 7. Meta-analysis of the effects of VPA on serum 25(OH)D3 level.

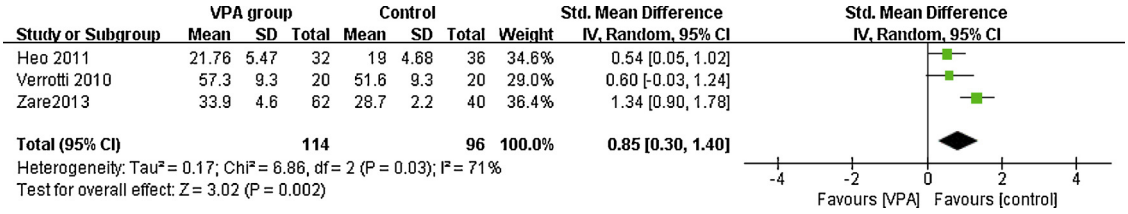

Fig. 8. Meta-analysis of the effect s of VPA on serum BALP level.

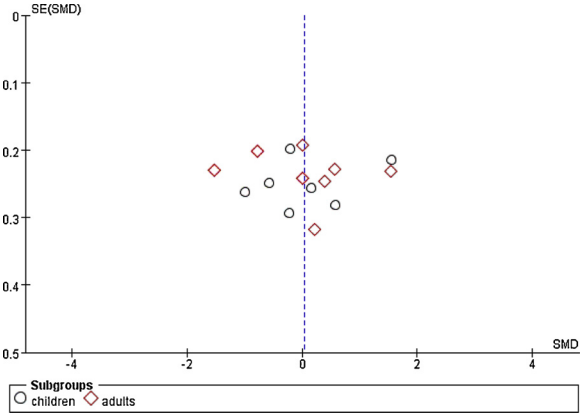

Fig. 9. Funnel plot of the effects of VPA on serum calcium level.

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Ethical approval

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

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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