BRIEF OVERVIEW ABOUT ASSOCIATION BETWEEN VITAMIN D AND EXERCISE EFFECTS WITH EPILEPSY

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Abstract

Antiepileptic medication use is associated with an increased risk of bone metabolism issues, decreased bone mineral density, and two to three times the risk of fractures in children and adolescents compared to healthy controls. We combed through the research on vitamin D treatment in children taking anti-epileptic medications and bone mineral density in children diagnosed with epilepsy. Research on bone mineral density markers in epileptic children has often shown no statistically significant change. Some studies have used too small of a sample size, while others have failed to account for potential confounding variables like obesity, comorbidities, poor diet, or lack of movement. Vitamin D therapy studies in children with epilepsy have been underwhelming and have failed to account for potential confounding variables due to a lack of stratification. In order to better understand the effects of polytherapy, decreased mobility, and symptomatic generalised epilepsy on fractures and other clinically important outcomes, larger studies are required. Vitamin D therapy may help children with epilepsy whose bones are at risk for poor health, however there is currently no solid data to support this claim. It is crucial for neurologists to prescribe low-dose vitamin D supplementation and monitor compliance in children with epilepsy, since this is now recommended for healthy children and there is biological evidence to suggest that children with epilepsy may be more likely to experience clinically significant deficiencies. Due to its effects on blood calcium levels, dopamine generation, and regulation of many brain functions, exercise is considered a safe, non-pharmacological method of treating the brain. The stimulation of antioxidant and anti-inflammatory pathways further enhances its neuroprotective activity. Multiple studies have shown that many other factors contribute to epileptogenesis. Epigenetic mechanisms impact the pattern of transcriptomics, proteomics, metabolomics, and exposomics by modifying chromatin structure through processes such as DNA methylation, acetylation, deacetylation, ubiquitination, and histone phosphorylation. Epileptogenesis is closely associated with these processes.

Keywords: Vitamin D, Exercise, Epilepsy

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Introduction:

In the United States, an estimated 9% of children between the ages of 1 and 21 have vitamin D insufficiency (serum vitamin D levels below 15 ng/mL). [1] Vitamin D deficiency, antiepileptic medication use, and poor bone health in people with epilepsy were first identified in 1979[2]. This link is believed to be especially important during youth, when bone mineralization is at its peak. Side effects of antiepileptic medication treatment in children and adolescents include altered bone metabolism, decreased bone mineral density, and a risk of fractures that is two to three times higher than in healthy controls. [5]. Hypotheses have been advanced suggesting that this could be due to the influence of the ketogenic diet and antiepileptic medications, as well as other variables such obesity, poor diet, and mobility. Possible causes of bone issues include calcium absorption problems, increased vitamin D breakdown in the liver due to cytochrome p450 activation and stimulation of osteoclastic activity, effects on bone cells directly, resistance to parathyroid hormone, and suppression of calcitonin production. [6]

Less than half of clinicians examine their epileptic patients for vitamin D levels and bone health, indicating a significant difference.

[7] There is a lack of consistency in the current guidelines. It should be noted that the International Society for Clinical Densitometry has not specifically included epilepsy as a reason to evaluate bone mineral density in children in its most recent position development statement [8]. Despite the availability of recent randomised controlled trials, a 2009 Cochrane review[9] concluded that there was insufficient evidence to warrant the routine administration of vitamins to individuals suffering from epilepsy. Vitamin D supplementation should begin at 400 IU for all infants and continue into puberty, according to the American Academy of Pediatrics; however, the organisation does not specify a dosage for adolescents using antiseizure medications. A recent meta-analysis of randomised controlled trials found that vitamin D supplementation does not improve bone mineral density in healthy children and adolescents [11], but it may be clinically advantageous for children who are low in the vitamin [12].

Bone Mineral Density among Children with Epilepsy

Table 1 lists 26 articles which are studies of markers of bone health in children with epilepsy. There are 14 cohort studies comparing bone mineral density and/or bone biochemistry in children treated with antiepileptic drugs and healthy controls. Of these, seven studies found a significant difference, four found no significance, and three studies did not comment on the statistical significance of any difference between the groups. There are 12 cohort studies observing bone mineral density and/or bone biochemistry in children treated with antiepileptic drugs. These found a prevalence of 25-OH vitamin D levels less than 20 of between 25% and 75% in children treated with antiepileptic drugs (with varying degrees of ambulation, duration of epilepsy, and number of antiepileptic drugs). There is great variation between studies in terms of controlling for confounding factors (e.g. mobility and diet).

Table 1: Studies of bone mineral density markers in children with epilepsy

Citation	Study group	Study type	Outcome	Key result	Comments
Shellhaas[4]	78 CWE (24% CP), 45% symptomatic, 24% daily seizures; 90% ambulatory; 10% tube feeding; 75% on AED>24 m, 22% old AED, 49% new	Retrospective cohort	25OH-D	Prevalence of 25OH-D<20 25%; 20-31 50%	Heterogeneous group
Rauchenzauner[13]	85 CWE VPA; 40 CWE other AEDs; 41 controls; treated>6 months; CP and immobile excluded	Retrospective cohort	Bone biochemistry	No 25OH-D<25	No significant difference in bone biochemistry between groups
Fuleihan[3]	88 CWE treated with various AEDs, 111 healthy controls	Retrospective cohort	DEXA lumbar spine and total body; 25OH-D	Prevalence of 25OH-D<20 57% in CWE; 79% in controls	No significant difference in BMD between CWE and controls
Cansu[14]	34 CWE newly diagnosed	Prospective	25OH-D; bone biochemistry	Significantly decreased 25OH-D; at 18 months post starting AED	No significant difference in BMD after AED treatment
Nettekoven[15]	38 CWE; 44 healthy; various AEDs	Cross-sectional observational	25OH-D, bone biochemistry	Prevalence of 25OH-D<20 75%; 25OH-D<30 21%; significantly abnormal osteocalcin, alkaline phosphatase; ICTP	Difference between CWE and controls not statistically assessed
Bergqvist[16]	45 CWE treated with ketogenic diet	Prospective cohort	25OH-D and PTH before and during ketogenic diet	Before ketogenic diet prevalence of 25OH-D<20 4%; 25OH-D<25 51%; at 3 m significantly increased 25OH-D; 15 m significantly decreased 25OH-D	Subgroup of CWE with refractory epilepsy; difficult to extrapolate; difficult to interpret decreased 25OH-D at 15 m
Sheth[17]	13 CWE LMG; 40 CWE polypharmacy; 36 healthy controls	Retrospective cohort	DEXA Total BMD	Significantly decreased BMD in polypharmacy group	Significant result found in very small subgroup
Bertoli[18]	17 CWE (refractory); 40% malnourished; 24% wasted	Retrospective cohort	DEXA	3 children osteopoenic; 1 osteoporotic	Very small sample
Tekgul[19]	15 CWE VPA; 11 CWE CBZ; 4 CWE PHB	Prospective cohort	DEXA lumbar spine, 25OH-D, bone biochemistry	6.7% BMD < –1.5	Small sample
Babayigit[20]	23 CWE treated with CBZ, 31 VPA, 14 oxCBZ; 30 controls	Retrospective cohort	DEXA, bone biochemistry	Significantly abnormal biochemistry; decreased BMD	Small sample
Nicolaidou[21]	51 CWE treated with CBZ/VPA; 80 controls	Prospective cohort	Bone biochemistry pre AEDs and every 3 m	49% acquired 25OH-D insufficiency within 3 years	Relatively large cohort study
Voudris[22]	22 CWE treated with CBZ	Prospective cohort	Bone biochemistry at 3, 6, 12 months treatment	Significantly raised alkaline phosphatase at 12 m	Small sample.
Ecevit[23]	17 CWE treated with CBZ>6 m; 16 CWE VPA>6 m; 31 controls	Retrospective cohort	DEXA neck of femur	Significantly decreased BMD in VPA group	Small subgroup analysis
Oner[24]	33 CWE VPA>6 m	Cross-sectional	DEXA lumbar spine, neck of femur, greater trochanter; bone biochemistry	Significantly raised osteocalcin; decreased BMD neck of femur and greater trochanter	Clinical significance uncertain as no comparison or follow up
Verrotti[25]	60 CWE CBZ 2 years; 60 healthy controls	Prospective cohort	Bone biochemistry, 25OH-D	Significantly more abnormal bone biochemistry in CWE	Significant difference found in bone biochemistry; mean serum 25-OH vitamin D<30 ng/mL in both groups
Tsukahara[26]	18 CWE	Cross-sectional	DEXA lumbar spine, bone biochemistry	BMD 9% less than normal; 5 patients had z-score <–1.5; some bone biochemistry markers abnormal	Small prevalence study
Farhat[27]	29 CWE treated with various AEDs for>6 m	Retrospective cohort	DEXA lumbar and thoracic spine, 25OH-D	Prevalence of 25OH-D deficiency 35%; insufficiency 27%	Prevalence study. heterogeneous group
Guo[28]	53 CWE treated with VPA/LTG/both	Retrospective cohort	DEXA, bone biochemistry	Prevalence of z-score <–1.5 24.4%	Prevalence study. heterogeneous group
Kafali[29]	13 CWE treated with VPA>6 m; 6 CWE treated with CBZ>6 m; 57 controls	Retrospective cohort	DEXA lumbar spine, radius, ulna; bone biochemistry	Significantly decreased BMD and increased alkaline phosphatase in VPA group	Small sample
Akin[30]	25 CWE VPA>1 y; 28 CWE CBZ>1 y; 26 controls	Retrospective cohort	DEXA lumbar spine	No significant difference between groups	No significant difference; no control for ambulation/diet
Baer[31]	Children age 3-9; 226 healthy, 23 ambulant CWE on AEDs, 43 nonambulant children, 46 nonambulant CWE on AEDs	Retrospective cohort	BMD, vitamin D	Significant difference in vitamin D and BMD between ambulant and nonambulant children	Effect of ambulation status on bone health significant after correcting for AED status
Sheth[32]	13 CWE treated with CBZ>18 m; 13 CWE treated with VPA>18 m; 27 healthy	Retrospective cohort	DEXA lumbar spine, radius	BMD significantly lower in VPA gp than controls	Small sample
Chung[33]	78 CWE treated with PHT/PHB; 78 controls	Cross-sectional	DEXA	No significant difference in BMD between CWE and controls; significant decrease in BMD all areas between CWE subgroups treated>24 m and<12 m	Subgroup analysis suggests possible link between duration of AED treatment and BMD loss
Weismann[34]	12 CWE treated with PHB; 13 treated with diphenylhydantoin; 25 treated with both	Cross-sectional	25OH-D	Significantly lower 25OH-D levels in CWE	Small sample
Winnacker[35]	41 CWE, 39 controls	Cross-sectional	Bone biochemistry	Significantly increased alkaline phosphatase in CWE	Suggestive of increased risk of osteopoenia in CWE
Hunter[36]	105 CWE treated with various AEDS	Cross-sectional	Bone biochemistry	Prevalence of hypocalcaemia 30%; raised alkaline phosphatase 24%	Heterogeneous group wrt type/ duration of AED, diet, mobility

CWE: Children with epilepsy, AED: antiepileptic drug; DEXA: Dual-energy X-ray absorptiometry, BMD: Bone mineral density, PHB: Phenobarbitone, PTH: Parathyroid hormone, LMG: Lamotrigine, CBZ: Carbamazepine, PHT: Phenytoin, CP: Cerebral palsy, VPA: Sodium valproate, ICTP: Pyridinoline cross-linked carboxyterminal telopeptide of type I collagen

Table 2 shows six studies of vitamin D therapy in children treated with antiepileptic drugs (AEDs). The only randomized controlled trial[37] was limited in terms of duration of therapy, lack of controlling for diet/exercise, and lack of study of compliance despite not attaining target vitamin D levels. It demonstrated no significant difference between high- and low-dose vitamin D, and no change in bone mineral density compared to healthy controls after 1 year of treatment. This may be a better outcome than in unsupplemented children with epilepsy whose bone mineral density has been shown to decrease with time in previous studies. Two cohort studies showed a significant increase in bone mineral density (one large and one small), two cohort studies showed a significant improvement in bone biochemistry, and one cohort study showed a significant improvement in bone biochemistry and healing of rickets with vitamin D therapy. Three of the six studies used bone biochemistry as an indirect marker of bone health, rather than bone mineral density.

It is difficult to compare the bone mineral density improvements as the studies use different units rather than a standardized *z*-score. As there is little description of comorbidities (the RCT is the only study to give a detailed description of comorbidities), there is potential for confounding with regard to comorbidities, such as mal-absorptive disorders, treatment with drugs other than AEDs which may affect bone health, nutrition, and immobility in those studies not pre-selecting an immobile group.

Table 2: Studies of vitamin D therapy in children with epilepsy

Citation	Study group	Study type	Outcome	Key result	Comments
Mikati[37]	78 Lebanese CWE aged ≥10; AED ≥6 m (mean 5.4 y); given 400 iU/d vs 2,000 iU/d; 111 controls given placebo. Several co-morbidities affecting bone health excluded (e.g., multiple fractures, other medications affecting bone health; mal-absorption)	RCT	DEXA lumbar spine and total body; 25OH-D	Small significant relative increase in subtotal body BMD after 1 year high-dose vitamin D therapy (mean 3.2% in high-dose group compared to 2.3% in low dose group)	Groups similar with regard to duration of AED therapy. No analysis of co-morbidities given although several co-morbidities excluded. Groups not balanced with regard to diet or exercise. Compliance not studied although target vitamin D level not reached
Tekgul[19]	56 CWE; AEDs (various number) for ≥2 years; given 400 iU/d vitamin D	Observational	Lumbar spine DEXA	5% of group had BMD <−1.5	Small group, heterogeneous with regard to AEDs, no comparison group
Jekovec[38]	23 CWE with spastic quadriplegic cerebral palsy, severe learning disability, bedridden, dependent on assisted feeding; treated with AEDs; of which 15 given 9 m vitamin D 0.25 mcg od and calcium 500 mg od; 8 controls	Cohort study	DEXA before and after vitamin D	Lumbar spine BMD significantly increased by mean 0.476 g/cm^2 in treated; decreased by mean 0.315 g/cm^2 in untreated	Confounding due to non-ambulant cohort. No association between duration of AED treatment and BMD. Small sample; no description of co-morbidities
Fischer[39]	11 CWE (non-ambulant and gastrostomy fed) age 7-17 given 4,000 iU/m^2/d for 6 m	Cohort	DEXA	Small significant increase in bone mineral content as percent of normal by 1.1% after 6 m treatment compared to baseline	Confounding due to non-ambulant cohort studied. Small and high-risk cohort
Offermann[2]	83 CWE treated with AEDs; 40 controls (people with learning disability in similar living conditions); given 9 m vitamin D at 37.5 mcg/week, 125 mcg/week, or 250 mcg/week	Cohort	Bone biochemistry	Significant improvement in biochemistry in 125 and 250 mcg/week groups	Small numbers in each group
Liakakos[40]	20 CWE untreated-12 treated with PHB (gp1), 8 treated with PHB and 2 m 4,000 iU/d vitamin D (gp2); 16 CWE age 6 m-7y who "did not suffer from ailments other than epilepsy" treated with PHB-8 given stat dose 200000 iU vitamin D (gp3); 8 given 4,000 iU/d for 2 m (gp4)	Cohort	Bone biochemistry (serum alkaline phosphatase and urine hydroxylproline pre treatment and every 15d; wrist XR	Significant increase in bone biochemistry markers in gp 1 and decrease in gp 4. All wrist X-rays normal.	Small numbers in each group. No analysis of effect of duration of AED treatment. No detailed information regarding co-morbidity other than statement "did not suffer from ailments other than epilepsy"
Silver[41]	Study 1: 59 CWE, half given 3 m 200 iU/d vitamin D; half given 3 m placebo. Study 2: 33 CWE treated with AEDs given 3,000 iU/wk vitamin D for 12 weeks, compared with 32 controls-"children not receiving drugs"	Cohort	Alkaline phosphatase; wrist X-ray	Significant decrease in alkaline phosphatase in treated groups; healing rickets in high dose treatment group	In study 1, 3 children had radiological rickets after 12 weeks but unclear which group they were in-potential confounding. In study two characteristics of controls little described

CWE: Children with epilepsy, AED: antiepileptic drug, DEXA: Dual-energy X-ray absorptiometry, BMD: Bone mineral density, PHB: Phenobarbitone, RCT: Randomised controlled trial

Most of the studies of bone mineral density markers in children with epilepsy [Table 2] have found little significant difference in bone mineral density markers in children with epilepsy. However, these studies may be biased as most included a small sample, and did not include large enough numbers to enable comparison between specific antiepileptic drugs or therapies, or between different epileptic syndromes. Of those studies in which this comparison was attempted, a significant association between sodium valproate and markers of poor bone health was found; but as this was only in small numbers, it might represent a spurious association that has not been excluded. In addition, many of the studies did not correct for confounding factors such as mobility, nutrition, and obesity. One small study that considered the effect of ambulatory status [32] did however, find a significant difference in bone health between ambulant and non-ambulant children. Studies of

vitamin D therapy in children with epilepsy have been similarly limited by lack of stratification with regard to factors that influence bone health such as comorbidities, nutrition, obesity, and mobility. Hence although there is little evidence for an effect, there is limited evidence for no effect. The only randomized controlled trial[14] was limited in terms of duration of therapy, lack of controlling for diet/exercise, and lack of study of compliance despite not attaining target vitamin D levels.

Hippocrates once said that "walking is man's best medicine." Physical activity is currently defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Given its prophylactic and curative effects on a wide range of physical ailments, such as neurological, metabolic, cardiovascular, and respiratory diseases, musculoskeletal problems, and cancer, exercise is now widely regarded as medicine [42]

Benefits of exercise:

Different illnesses that affect the human body are not only bad for people's health, but they can also lower quality of life. The reduction in national physical fitness is mostly due to the lack of physical activity in modern living [43]

It influences adults' physical well-being and productivity at work as well as children's and teenagers' growth and development. Additionally, a lack of exercise increases the likelihood of developing chronic diseases[44]

According to research, a moderate exercise programme can boost energy expenditure, build muscle, lower blood pressure and blood cholesterol levels, raise bone density, and control psychological processes [45]

Exercise and inflammation

Chronic systemic inflammation predisposes individuals to insulin resistance, endothelial cell dysfunction, and exacerbates neuroinflammation, thereby contributing to neuropathological changes in the brain [46]

Exercise is advocated as a powerful anti inflammatory therapy for depression and neurodegeneration diseases. High level of TNF-α is linked to poor response to antidepressive effects of exercise in major depressive disorder [47]

Evidence suggested that exercise could protect the brain from inflammation, either by directly mediating inflammatory cytokines or reducing pro-inflammatory adipokines, thereby rescuing the secretion of growth factors and promoting neural plasticity and neurogenesis. Furthermore, exercise has also been suggested to mediate the innate inflammatory response through the sympathetic nerves or the hypothalamic-pituitary-adrenal axis as a physiological stressor**.** The direct effect of exercise on inflammation can be varied depending on the different pathophysiological conditions of individuals, since both pro-inflammatory cytokines and anti-inflammatory cytokines were increased immediately in the circulation after exercise [48]

Exercise-Induced Cardiovascular Benefit

Regular physical activity is important for maintaining a healthy lifestyle, with numerous cross-sectional studies confirming a decreased overall risk of cardiovascular illnesses and cardiac events linked to routine or recreational physical activity[49]

Because of the exercise-induced cardiovascular effect, regular physical activity is currently being used to treat cardiovascular morbidity and mortality without the use of drugs[50]

Numerous cellular and molecular level hypotheses have been made regarding the cardiovascular benefits of exercise to date. These hypotheses include increased insulin sensitivity, decreased oxidative stress and adiposity, fibre transformation towards oxidative myofibers, and increased mitochondrial function [45]

Exercise and mental health

Numerous research examining the effects of mental health on physical performance and the effects of physical fitness on both mental performance and health give numerous proofs of concept for this theory in the scientific literature. [51]

Several epidemiological studies have shown that lower levels of physical activity or longer sedentary periods are linked to a higher risk of poor mental health. [46]

Exercise is recognized as a safe, non-pharmacological approach to treat the brain since it increases blood calcium levels, triggers dopamine production, and regulates several brain functions. Its neuroprotective function is further enhanced by the activation of antioxidant and anti-inflammatory pathways. [52]

These lines of evidence suggest that people with neurodegenerative disorders can benefit from exercise. Additionally, physical activity can reduce the signs of depression and enhance cognitive performance**.** Exercise also improves mood, lessens stress, and lowers the chance of depression. This has been linked to increased blood flow to the brain, the supply of nutrients and oxygen to neurons, and the removal of metabolic waste. According to **Allendorfer et al.** [53]**,** the production of BDNF is another conceivable

mechanism for how exercise protects neuron lifespan and improves cognitive performance.

Physical exercise and epilepsy

Physical activity and sports can be safely practised on a daily basis by people with epilepsy without endangering their safety or affecting the frequency of seizures, according to research[54]

People with epilepsy who have engaged in physical activity have increased their maximum aerobic capacity, work capacity, body composition, and self-esteem, leading to improvements in their psychological and social well-being [55]**.** Even before, during, and after physical activity, there is a higher generation of - endorphins and steroids, and their introduction into the bloodstream appears to change the aberrant neuronal electrical activity, reducing the frequency of crises [56]**.**

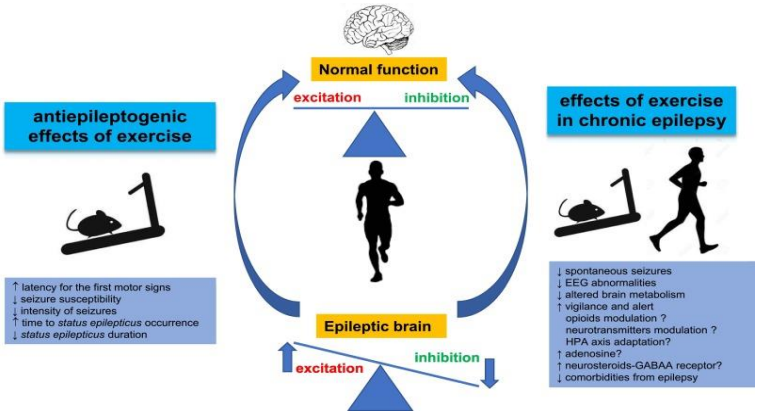

Figure (1) Physical exercise and seizure activity [57].

Physical exercise and epigenetic factors associated with epilepsy

Several researchs have demonstrated that a wide range of additional variables have a role in epileptogenesis. DNA methylation, acetylation, deacetylation, ubiquitination, and histone phosphorylation are examples of epigenetic mechanisms that alter the chromatin structure and influence the pattern of transcriptomics, proteomics, metabolomics, and exposomics. These mechanisms are strongly linked to epileptogenesis [57].

Epigenetic factors are also changed by exercise. Exercise enhances the expression of BDNF and improves brain function by increasing histone H3 acetylation and decreasing the expression of some histone deacetylases. Exercise also makes histone H3 more phosphoacetylated, which enhances cognitive performance [58].

Gene expression modification brought on by microRNAs is another epigenetic process**.** Epilepsy causes deregulation in a number of microRNAs**.** Regular exercise slows down neurodegeneration and reduces anxiety via altering the expression of microRNAs in the brain. However, further research is necessary to fully understand how physical activity affects the microRNAs in epileptic people's brains [59].

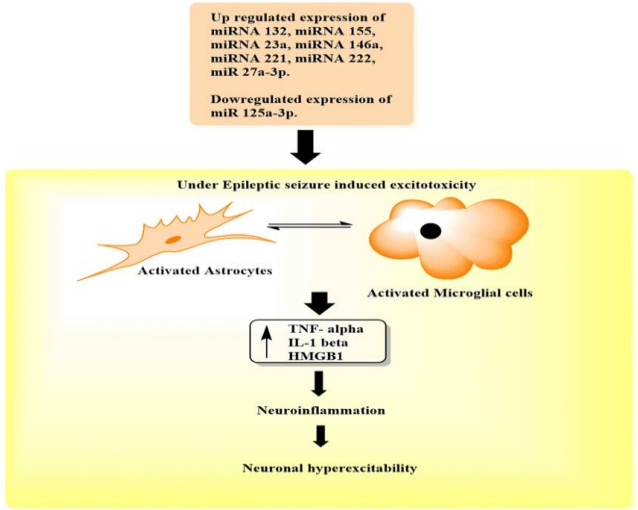

Figure (2) Alterations in microRNAs and neuroinflammation in epilepsy. [60].

Exercise and antiepileptic drugs

The concentration of antiepileptic drugs (AEDs) in the serum has not been shown to change significantly as a result of physical activity. However, physical activity alters the metabolism of some liver enzymes, which can reduce oxidative stress and the hepatotoxicity caused by AEDs. This is particularly true of the oxidative metabolic pathway, which is primarily activated during aerobic exercise**.** Interesting enough, the increased activity of this pathway during and after exercise and the resulting release of free fatty acids into the bloodstream may compete with the albumin transporter, a transporter for AEDs, leading to an increase in drug concentration in the blood**.** For instance, valproic acid, an AED, induces hepatotoxicity by causing mitochondrial malfunction and hepatocyte necrosis through the formation of reactive oxygen species (ROS). Exercise, on the other hand, boosts the expression of PGC-1 and reduces ROS by causing mitochondrial biogenesis in skeletal muscle [61].

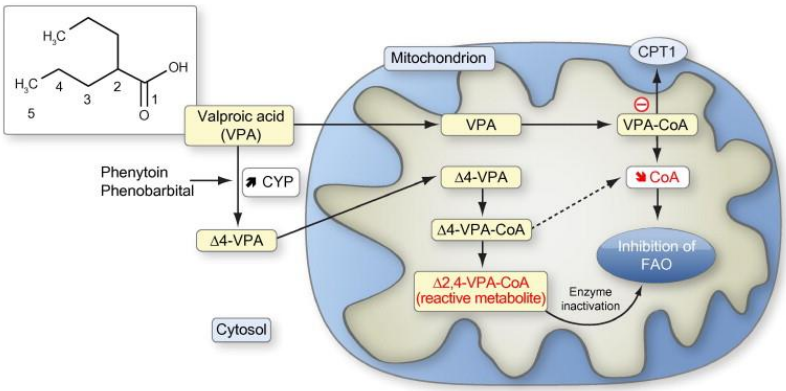

Figure (3) Mechanisms of valproic acid-induced inhibition of mitochondrial fatty acid β-oxidation. [62].

Conclusion

Studies to date are inconsistent and of limited quality. In particular, there is a need for larger studies, using clinically significant outcomes such as fractures, including at risk populations such as symptomatic generalised epilepsy, impaired mobility, and polytherapy. At the present time in the absence of good evidence to the contrary, there remains concern that children with epilepsy are at risk of poor bone health and that vitamin D therapy may be beneficial. As low-dose vitamin D supplementation (400 IU per day) is now recommended for healthy children and it is biologically feasible that children with epilepsy may be at higher risk of clinically significant deficiency, it is important that neurologists ensure that low-dose vitamin D supplementation should be prescribed and compliance followed up in children with epilepsy. Due to its effects on blood calcium levels, dopamine generation, and regulation of many brain functions, exercise is considered a safe, non-pharmacological method of treating the brain. The stimulation of antioxidant and anti-inflammatory pathways further enhances its neuroprotective activity. Multiple studies have shown that many other factors contribute to epileptogenesis. Epigenetic mechanisms impact the pattern of transcriptomics, proteomics, metabolomics, and exposomics by modifying chromatin structure through processes such as DNA methylation, acetylation, deacetylation, ubiquitination, and histone phosphorylation. Epileptogenesis is closely associated with these processes.

No Conflict of interest.

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