American Journal on Intellectual and Developmental Disabilities

Bone mineral density screening in people with epilepsy and intellectual disability

--Manuscript Draft--

Manuscript Number:	AJIDD-D-23-00067R3
Article Type:	Research Report
Keywords:	epilepsy; Intellectual disabilities; vitamin D; bone mineral density
Corresponding Author:	Revital Gandelman-Marton Shamir Medical Center Assaf Harofeh Zerifin, ISRAEL
First Author:	Revital Gandelman-Marton
Order of Authors:	Revital Gandelman-Marton
	Jacques Theitler
Manuscript Region of Origin:	ISRAEL
Abstract:	Vitamin D measurements and dual energy x-ray absorptiometry (DXA) scans are recommended in people with intellectual disability and/or epilepsy in order to prevent bone-linked harm. The prevalence of vitamin D supplementation and bone mineral density screening were evaluated in 68 people with epilepsy and intellectual disability (EID) and 68 matched controls with epilepsy without intellectual disability. DXA scan was not performed in any of the people with EID while performed in 11.8% of the people in the control group. People with EID had a higher vitamin D supplementation rate, and were treated with more antiepileptic drugs (AEDs) and more AED combinations including first generation AEDs. Increased awareness of bone health screening in people with epilepsy and especially EID is warranted.

Bone mineral density screening in people with epilepsy and intellectual disability

Revital Gandelman-Marton[1,2], Jacques Theitler[1,2]

[1]Neurology Department, Shamir-Assaf Harofeh Medical Center, Zerifin, and [2]Faculty of Medicine, Tel Aviv University, Israel

Running title: Bone health in people with epilepsy and intellectual disability

Funding: None

Conflict of interest: None

All correspondence: Prof. Revital Gandelman-Marton,
Department of Neurology
Shamir- Assaf Harofeh Medical Center
Zerifin 70300
Israel
Tel.:972-8-9778134
Fax: 972-8-9779758
Email:revitalgm@hotmail.com

Abstract

Vitamin D measurements and dual energy x-ray absorptiometry (DXA) scans are recommended in people with intellectual disability and/or epilepsy in order to prevent bone-linked harm. The prevalence of vitamin D supplementation and bone mineral density screening were evaluated in 68 people with epilepsy and intellectual disability (EID) and 68 matched controls with epilepsy without intellectual disability. DXA scan was not performed in any of the people with EID while performed in 11.8% of the people in the control group. People with EID had a higher vitamin D supplementation rate, and were treated with more antiepileptic drugs (AEDs) and more AED combinations including first generation AEDs. Increased awareness of bone health screening in people with epilepsy and especially EID is warranted.

Key words: Epilepsy; intellectual disabilities; vitamin D; bone mineral density

1. Introduction

People with intellectual disability (ID) or epilepsy are at increased risk of falls and fractures compared with the general population [Axmon et al. 2019; Miller et al. 2020]. Falls can occur outdoors and during vital indoor activities in people with ID, and were reported at younger ages compared to the general population [Axmon et al. 2019; Miller et al. 2020; Schrager et al. 2007]. In people with epilepsy, fractures can occur especially during generalized convulsive seizures, and the risk of falls and subsequent fractures can be increased by side-effects of antiepileptic drugs (AEDs), such as ataxia and sedation, especially in people with reduced bone mineral density (BMD) [Grzonka et al. 2019;Pack 2011; Winterhalder R, Shankar R. 2022].

Low BMD and vitamin D deficiency are independent risk factors for fractures. Vitamin D stimulates calcium absorption and influences bone mineralization and turnover, thus preventing osteomalacia and benefiting skeletal development in children and adolescents, as well as improving musculoskeletal and neuromuscular coordination in adults and decreasing risk of falls [Grant et al. 2015]. Generally, BMD is affected by hereditary factors, including gender and ethnicity. Decreased BMD was associated with age, hormonal status, alcohol, smoking, and lack of nutrition or exercise, and was also related to ID level, decreased ambulation, and AEDs [Winterhalder et al. 2022]. People with ID or epilepsy have high prevalence of vitamin D deficiency and high rates of decreased BMD [Bastiaanse et al. 2014; Frighi et al. 2014; McKinnon et al. 2018; Winterhalder et al. 2022], and these are even higher in people with both ID and epilepsy [Berkvens et al. 2021; Winterhalder et al. 2022]. Although there is no agreement on normal 25(OH)D levels, there is consensus that levels lower than < 20 ng/mL in adults are associated with osteomalacia or osteoporosis, proximal limb muscle weakness and increased risk of fractures [Cesareo

et al. 2018]. Screening for vitamin D deficiency is recommended in individuals at risk, including- among others- those with osteomalacia, osteoporosis, history of falls or non-traumatic fractures, treatment with AEDs, and people with insufficient sun exposure [Cesareo et al. 2018].

In the general population, BMD screening is recommended for women ≥65 years old or for younger ages in the presence of risk factors (i.e. prior history of fracture or rheumatoid arthritis, use of glucocorticoid steroids, tobacco or alcohol, family history of osteoporosis and fracture) [Pack 2011; Winterhalder et al. 2022]. In people with ID, it is recommended to begin BMD screening at younger ages [Dreyfus et al. 2014]. In people with AED- treated epilepsy, it is recommended to counsel about adequate vitamin D intake, consider routine 25-hydroxyvitamin D screen especially when treated with enzyme-inducing AEDs, and to obtain a dual energy x-ray absorptiometry scan (DXA scan) to measure BMD in people with increased fracture risk, including long-term AED exposure, especially in the presence of other risk factors [Berkvens et al. 2021;Pack 2011].

In this study, we aimed to evaluate the prevalence of vitamin D supplementation and BMD screening in people with epilepsy and intellectual disability (EID) who presented to their first visit in our epilepsy clinic.

2. Patients and methods

The study was approved by the Ethics Committee at our Medical Center.

The computerized medical information management system was searched for the summary of the first epilepsy clinic visit during a 10-year period (2012 - 2021). Sixty-eight people with EID were identified and were compared to a control group that included 68 people with epilepsy without ID, matched for age, gender, and epilepsy

type and duration.

The visit summaries were retrospectively reviewed for the following data: age, gender, reason for visit, epilepsy type and duration, number and type of current AEDs, number of previous AEDs, presence of vagus nerve stimulator (VNS), status of vitamin D consumption and performance of DXA scan. Seizure types and epilepsy syndromes were classified based on criteria of the International League Against Epilepsy [Scheffer et al. 2017]. AED type was classified according to AED generation as following: first generation (phenytoin, carbamazepine, valproic acid, phenobarbital, clonazepam, sultiame, primidone, ethosuximide), second generation (lamotrigine, topiramate, levetiracetam, gabapentin, oxcarbazepine, zonisamide, vigabatrin, felbamate), third generation (lacosamide, perampanel, brivaracetam, stiripentol, clobazam), polytherapy including a first generation AED, and polytherapy of second and third generation AEDs.

Statistical analysis was done by SPSS version 27.0, Chicago, IL. Categorical variables were analyzed using Pearson χ^2 test (reason for first visit, AED type) and Fisher's Exact test (gender, epilepsy type, treatment with vitamin D, performance of DXA scan, presence of VNS), and t test was used to analyze continuous variables (age, epilepsy duration, number of previous and current AEDs). Statistical significance was determined at $p<0.05$.

3. Results

The study groups included 136 people with epilepsy aged 18 to 61 years (mean- 25.8 years), 82 (60.3%) men, 40 (29.4%) with generalized and 96 (70.6%) with focal epilepsy. Epilepsy duration ranged between 0.1 to 50 years (mean- 18 years). Seventy-six (55.9%) people were referred to the clinic with questions regarding management (change of AED dosage or type, AED discontinuation, epilepsy surgery,

VNS), 22 (16.2%) - following admission, and 38 (27.9%) people were transferred from neuropediatric follow-up**.** Sixty-four (47.1%) people were treated with AED monothearpy, 43 (31.6%) received two AEDs, and 29 (21.2%) people were treated with a polytherapy of 3 to 7 AEDs. Thirteen (9.6%) people had a VNS. Eighty-six (63.2%) people received first generation AEDs or a polytherapy of first and second and/or third AEDs, and 50 (36.8%) were treated with second- and/or third generation AEDs. Fifty-one (37.5%) people were previously treated with 1 -2 AEDs, 45(32.9%) - with 3-15 AEDs, and 40 (29.4%) people had no previous AEDs.

People with ID were treated in general with more AEDs (2.2 vs 1.5) (p=0.001) and more polytherapies that included first generation AEDs (45.6% vs 20.6%) (p=0.009). Vitamin D supplementation rate was higher among people with EID (18(26.5%) vs 8(11.8%)) (p=0.048). None of the people with EID had a DXA scan while performed in 8 (11.8%) people without ID (p=0.006).

4. Discussion

In this study we evaluated the prevalence of vitamin D supplementation and BMD screening in people with epilepsy and with or without ID. We found that a DXA scan was performed in a small percentage of the people without ID who presented for their first visit in our epilepsy clinic and in none of the people with EID.

Challenges in accessing appropriate investigations are one of the areas of concern in the diagnosis and medical treatment of people with EID [Kerr et al. 2014]. Most people with ID can tolerate blood tests and cooperate with a DXA scan [Berkvens et al. 2021; Frighi et al. 2019; Winterhalder et al. 2022]. According to the 2007 practice guideline of the International Society for Clinical Densitometry, an alternative test (i.e. quantitative ultrasound) can be used to assess fracture probability in people who cannot cooperate to perform a DXA scan [Krieg et al. 2008;Winterhalder et al. 2022],

however, only modest associations with DXA BMD measurements were demonstrated in later analyses [Shalof et al.. 2021; Swinton et al. 2023].
In previous studies, BMD screening was performed in 23% of adults with ID (34% of women, 13% of men), significantly lower than screen rates in the general population [Dreyfus et al. 2014]. Factors associated with having a BMD screen included use of vitamin D or AED, living in a 24-hour supported residential setting, and recent receipt of a flu vaccine, and decreased likelihood of screening was associated with diagnosis of Down syndrome [Dreyfus et al. 2014]. It was suggested that the low rate of BMD screening in people with ID may be related to low awareness of health providers and possibly of people with epilepsy and ID and their carers of the increased osteoporosis risk in this population [Dreyfus et al. 2014; Sawhney et al. 2020],

In our group, vitamin D supplementation rate was higher in people with EID. It is possible that vitamin D deficiency rate was higher in people with both epilepsy and ID, as previously reported [Bastiaanse et al. 2014; Frighi et al. 2014; McKinnon et al. 2018; Winterhalder et al. 2022], and cannot be ascertained by our limited data regarding pre-supplementation 25-hydroxyvitamin D serum levels. It is also possible that people were supplemented with vitamin D when a DXA scan was deemed infeasible, and this was more likely in people with- compared to those without ID [Winterhalder et al. 2022]. Another possible explanation is that the increased access to preventive care in people with EID lead to higher rate of vitamin D supplementation in this group [Dreyfus et al. 2014].

Sixty-six percent of our people with EID received first generation AEDs and were treated with significantly more polytherapies that included first generation AEDs compared to people without ID. First generation AEDs are frequently used to treat epilepsy in people with ID despite their adverse effects on bone health and many are

exposed to AED polytherapy [O'Dwyer et al. 2018; Snoeijen-Schouwenaars et al. 2021]. Negative effects on bone health were consistently reported for phenytoin, phenobarbital and primidone, and there are mixed reports regarding carbamazepine and valproate [Pack 2011]. AED polytherapy was associated with increased fracture risk, related both to decreased BMD and to dose dependent effect on the central nervous system [Baddoo et al. 2021; Souverein et al. 2006; Tsiropoulos et al. 2008; Vestergaard et al. 2004]. Data regarding second and third generation AEDs are limited. Oxcarbazepine can reduce vitamin D metabolites [Cansu et al. 2008; Mintzer et al. 2006]. Lamotrigine effects on bone are limited but there are conflicting reports [Gou et al. 2001; Kim et al. 2007; Pack et al. 2008]. Topiramate and zonisamide can cause renal acidosis, both associated with secondary bone abnormalities [Pierce et al. 1991]. Levetiracetam was found to affect bone quality in animal studies [Nissen-Meyer et al. 2007]. Although decreased BMD and increased fracture risk were mostly associated with enzyme-inducing AEDs, other mechanisms may be implicated, including inhibition of intestinal calcium absorption, osteoclast cell growth, cellular response to parathyroid hormone and calcitonin secretion, hyponatremia-induced osteoporosis, direct effects on bone cells and bone turnover markers, and AED adverse effects (i.e. dizziness, unsteadiness, confusion) [Diemar et al. 2019; Fan et al. 2016; Winterhalder & Shankar, 2022].

This retrospective study has several limitations. We had no data on the type of previous AEDs, and it is possible that these influenced current vitamin D supplementation status. This study focused on the performance of DXA scan according to treatment guidelines in this population. We had no access to data regarding vitamin D nutritional status (i.e. intake, supplementation dose and duration) and BMD moderating factors, and had only partial results of 25-hydroxyvitamin D

serum levels and DXA scans, and therefore, could not evaluate whether vitamin D dose was effective in achieving a sufficient vitamin D status. Finally, this was a single-center study and our results need to be externally validated.

In conclusion, this study shows that contrary to current recommendations, people with EID were not undergoing the same investigations as people with epilepsy without ID. A detailed evaluation of vitamin D nutritional status and BMD moderating factors, and measurement of 25-hydroxyvitamin D serum levels and BMD may improve our care of patients with epilepsy and EID. Further studies are needed to identify measures that can increase awareness of bone health screening in people with epilepsy and especially EID among physicians and caretakers.

References

Axmon A., Ahlström G. & Sandberg M. (2019) Falls resulting in health care among older people with intellectual disability in comparison with the general population. *Journal of Intellectual Disability Research **63**, 193-204*.

Baddoo D.R., Mills A.A., Kullab R.B., Al-Mashat H., Andersen N.B., Jorgensen N.R. et al. (2021) Metabolic bone disease in patients with epilepsy and the use of antiepileptic drugs - insight from a Danish cross-sectional study. *Seizure **86**:29-34*.

Bastiaanse L.P., Mergler S., Evenhuis H.M. & Echteld M.A. (2014) Bone quality in older adults with intellectual disabilities. *Research in Developmental Disabilities **35**:1927-33*.

Berkvens J.J.L., Wyers C.E., Mergler S., Beerhorst K., Verschuure P., Tan I.Y. et al. (2021) Incidence of clinical fractures: A 7-year follow-up study in institutionalized adults with epilepsy and intellectual disability. *Seizure **92**:56-61*.

Cansu A., Yesilkaya E., Serdaroğlu A., Hirfanoglu T.L., Camurdan O., Gülbahar O. et al. (2008) Evaluation of bone turnover in epileptic children using oxcarbazepine. *Pediatric Neurology* ***39****:266– 71*.

Cesareo R., Attanasio R., Caputo M., et al. (2018) Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. *Nutrient* ***10****:546.*

Diemar S.S., Sejling A.S., Eiken P., Andersen N.B. & Jorgensen N.R. (2019) An explorative literature review of the multifactorial causes of osteoporosis in epilepsy. *Epilepsy & Behavior* ***100****:106511*.

Dreyfus D., Lauer E. & Wilkinson J. (2014) Characteristics associated with bone mineral density screening in adults with intellectual disabilities. *Journal of the American Board of Family Medicine* ***27****:104-14.*

Fan H.C., Lee H.S., Chang K.P., Lee Y.Y., Lai H.C., Hung P.L. et al. (2016) The Impact of Anti Epileptic Drugs on Growth and Bone Metabolism. *International Journal of Molecular Sciences* ***17****:1242.*

Frighi V., Morovat A., Andrews T.M., Rana F., Stephenson M.T., White S.J. et al. (2019)Vitamin D, bone mineral density and risk of fracture in people with intellectual disabilities. *Journal of Intellectual Disability Research* ***63****:357-367.*

Frighi V., Morovat A., Stephenson M.T., White S.J., Hammond C.V. & Goodwin G.M. (2014) Vitamin D deficiency in patients with intellectual disabilities: prevalence, risk factors and management strategies. *The British Journal of Psychiatry* ***205****:458-64*.

Gou C.Y., Ronen G.M. & Atkinson S.A. (2001) Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. *Epilepsia **42**:1141–7.*

Grant W.B., Wimalawansa S.J., Holick MF, Cannell J.J., Pludowski P., Lappe J.M. et al. (2015) Emphasizing the health benefits of vitamin D for those with neurodevelopmental disorders and intellectual disabilities. *Nutrients **7**:1538-64.*

Grzonka P., Rybitschka A., De Marchis G.M., Marsch S. & Sutter R. (2019) Bone fractures from generalized convulsive seizures and status epilepticus-A systematic review**.** *Epilepsia **60**:996-1004.*

Kerr M., Linehan C., Thompson R., Mula M., Gil-Nagal A., Zuberi S.M. et al. (2014) A White Paper on the medical and social needs of people with epilepsy and intellectual disability: the Task Force on Intellectual Disabilities and Epilepsy of the International League Against Epilepsy. *Epilepsia **55**:1902-6.*

Kim S.H., Lee J.W., Choi K.G., Chung H.W. & Lee H.W. (2007) A 6- month longitudinal study of bone mineral density with antiepileptic drug monotherapy. *Epilepsy & Behavior **10**:291–5*.

Krieg MA, Barkmann R, Gonnelli S, et al. (2008) Quantitative ultrasound in the management of osteoporosis: the 2007 ISCD Official Positions. *Journal of Clinical Densitometry* **11**:163–87.

McKinnon I., Lewis T., Mehta N., Imrit S., Thorp J. & Ince C. (2018) Vitamin D in patients with intellectual and developmental disability in secure in-patient services in the North of England, UK. *BJPsych Bulletin **42**:24-29.*

Miller A.S., Ferastraoaru V. , Tabatabaie V., Gitlevich T.R., Spiegel R. & Haut S.H. (2020) Are we responding effectively to bone mineral density loss and fracture risks in people with epilepsy? *Epilepsia Open* ***5****:240-247*.

Mintzer S., Boppana P., Toguri J. & DeSantis A. (2006) Vitamin D levels and bone turnover in epilepsy taking carbamazepine or oxcarbazepine. *Epilepsia.47:510–5.*

Nissen-Meyer L.S.H, Svalheim S., Tauboll E., Reppe S., Lekva T., Solberg L.B. et al. (2007) Levetiracetam, phenytoin, and valproate act differently on rat bone mass, structure, and metabolism. *Epilepsia* ***48****:1–11*.

O'Dwyer M., Peklar J., Mulryan N., McCallion P., McCarron M. & Henman M.C. (2018) Prevalence and patterns of anti-epileptic medication prescribing in the treatment of epilepsy in older adults with intellectual disabilities. *Journal of Intellectual Disability Research* ***62****:245-261*.

Pack A.M. (2011) Treatment of epilepsy to optimize bone health. *Current Treatment Options in Neurology* ***13****:346-54*.

Pack A.M., Morrell M.J., Randall A., McMahon D.J. & Shane E. (2008) Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. *Neurology* ***70****:1586–93*.

Pierce Jr W.M., Nardin G.F., Fuqua M.F., Saban-Maren E., & Stern S.H. (1991) Effect of chronic carbonic anhydrase inhibitor therapy on bone and mineral density in white women. *Journal of Bone and Mineral Research* ***6****:347–54*.

Sawhney I., Zia A., Yazdi B., Shankar R. (2020) Awareness of bone health risks in people with epilepsy and intellectual disability. *British Journal of Learning Disabilities* ***48****:224-231*.

Scheffer IE, Berkovic S, Capovilla G, Connolly M.B., French J., Guilhoto L. et al. (2017) ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* ***58****:512-521*.

Schrager S., Kloss C. & Ju A.W. (2007) Prevalence of fractures in women with intellectual disabilities: a chart review. *Journal of Intellectual Disability Research* ***51****:253–9*.

Shalof H, Dimitri P, Shuweihdi F, Offiah AC.(2021) "Which skeletal imaging modality is best for assessing bone health in children and young adults compared to DXA? A systematic review and meta-analysis". *Bone* **150**:116013.

Snoeijen-Schouwenaars F.M., Young C., Rowe C., van Ool J.S., Schelhaas H.J. & Shankar R. (2021) People with epilepsy and intellectual disability: More than a sum of two conditions. *Epilepsy & Behavior* ***124****:108355*.

Souverein P.C., Webb D.J., Weil J.G., Van Staa T.P. & Egberts A.C.G. (2006) Use of antiepileptic drugs and risk of fractures: case-control study among patients with epilepsy. *Neurology* ***66****:1318–1324*.

Swinton PA, Elliott-Sale KJ, Sale C. (2023) Comparative analysis of bone outcomes between quantitative ultrasound and dual-energy x-ray absorptiometry from the UK Biobank cohort. *Archives of Osteoporosis* **18**:77.

Tsiropoulos I, Andersen M, Nymark T, Lauritsen J., Gaist D. & Hallas J et al. (2008) Exposure to antiepileptic drugs and the risk of hip fracture: a case-control study. *Epilepsia.****49****:2092–9*.

Vestergaard P., Rejnmark L. & Mosekilde L. (2004) Fracture risk associated with use of antiepileptic drugs. *Epilepsia* ***45****:1330–1337*.

Winterhalder R., McCabe J., Young C., Lamb K., Sawhney I, Jory C. et al. (2022) Bone health, intellectual disability and epilepsy: An observational community-based study. *Acta Neurologica Scandinavica* ***145****:753-761*.

Winterhalder R, Shankar R. (2022). Bone health in adults with epilepsy and intellectual disability. *British Journal of General Practice* **72**:100-101.

Table. Clinical, bone health and AED-related parameters

			Intellectual disability		*p*
			Individuals with (n=68)	Individuals without (n=68)	
Age			25.6±10.3	26±10.6	0.835
Gender (M/F)			41(60.3)/ 27(39.7)	41(60.3)/ 27(39.7)	1.000
Epilepsy type	Generalized		21(30.9)	19(27.9)	0.851
	Focal		47(69.1)	49(72.1)	
Epilepsy duration (years)			18.7±11	17.3±11	0.443
Reason for visit	Following admission		10(14.7)	12(17.6)	0.889
	Management*		39(57.4)	37(54.4)	
	Transfer from neuropediatric follow-up		19(27.9)	19(27.9)	
Current AEDs			2.2±1.2	1.5±0.8	0.001
Previous AEDs			2±2.5	2.5±2.7	0.225
AED type	1st generation		14(20.6)	22(32.4)	0.009
	2nd generation		21(30.9)	23(33.8)	
	3rd generation		0	4(5.9)	
	Polytherapy	including 1st generation	31(45.6)	14(20.6)	
		2nd & 3rd generation	2(2.9)	5(7.4)	

VNS	8(11.8)	5(7.4)	0.561
Vitamin D supplementation	18(26.5)	8(11.8)	0.048
DXA scan	0	8(11.8) §	0.006
25(OH)D serum level (ng/ml) §§	20.7±8.5 (n= 44)	20.9±7.1 (n= 38)	0.931
BMI	24±6.4 (n= 27)	25.9±5.6 (n= 29)	0.237

n (%)

AED- antiepileptic drugs, VNS- Vagus Nerve Stimulator

***** Management- questions regarding change of AED dosage or type, AED discontinuation, epilepsy surgery, VNS

§ Four individuals had osteopenia: spine (1), spine and forearm (1), unspecified body area (2). One individual had borderline spine & normal hip (1). Three scans were normal.

§§ Reference values: Deficiency < 10 ng/ml, insufficiency 10-30 ng/ml, sufficiency 30-100 ng/ml.