Bone health, intellectual disability and epilepsy: An observational community-based study

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Objectives: Intellectual disability (ID) and epilepsy are independent risk factors for osteoporosis. Diverse predisposing factors influence this, for example in ID, genetics and poor nutrition and in epilepsy, anti-seizure medication (ASM). Around 25% people with ID have epilepsy, majority treatment resistant. ASMs polypharmacy is common. However, little is known about the bone-related characteristics of this vulnerable group. A prospective observational cohort study of bone profile across a community ID Epilepsy service was undertaken to understand this.

Materials & Methods: Participants were on minimum 2 years of ASMs. Baseline demographics, epilepsy data, bone metabolism biomarkers, bone mineral density (BMD) and vitamin D levels were collected. Doses needed to correct vitamin D insufficiency/deficiency were calculated.

Results: At baseline, of 104 participants, 92 (90.2%) were vitamin D insufficient/deficient. Seventy-six (73.1%) had a DEXA scan, 50 of whom—in the osteopaenic/osteoporotic range. DEXA scores between ambulant and non-ambulant patients were significantly different ($p = .05$) but not for ID severity. A high alkaline phosphatase (ALP) predicted lower vitamin D levels. Borderline significance ($p = .06$) in calcium levels between normal and high ALP was identified. There were no significant associations between parathyroid hormone, inorganic phosphate and magnesium levels, with vitamin D status or DEXA hip T-scores. Normalizing vitamin D levels (mean 101.4 nmol/L) required an average of 1951IU cholecalciferol daily.

Conclusions: Vitamin D deficiency is highly prevalent in people with ID and epilepsy treated with ASMs impacting likely on their bone health. Screening with vitamin D levels, ALP and DEXA in this group should be pro-actively and routinely considered.

KEYWORDS
antiepileptic drugs, developmental neurology, quality of life, seizures, treatment

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There has been growing interest in the association between abnormalities of bone metabolism and epilepsy in recent years. Both low bone mineral density (BMD) and vitamin D deficiency are established independent risk factors for fracture.

Individual variability in BMD in 80% of people is explained by hereditary factors, including sex and ethnicity. Low levels of physical activity, smoking, alcohol and hormonal status (post-menopausal women and testosterone-deficient men) are also known to be associated with reduced BMD.

Vitamin D stimulates gastrointestinal absorption of calcium and influences bone mineralization and turnover rate; its lack predisposes to osteoporosis and fractures. Vitamin D deficiency can lead to osteopenia and osteoporosis, as well as osteomalacia in adults. The National Osteoporosis Society (NOS) recommends treatment for individuals with a serum vitamin D level below 25 nmol/L, and for those with a serum level between 25 and 50 nmol/L if they have any of the following: fragility fracture, osteoporosis, high fracture risk, symptoms suggestive of vitamin D deficiency or increased risk of developing vitamin D deficiency including raised serum parathyroid hormone, and treatment with anti-seizure medication (ASM).

Most vitamin D under normal circumstances is synthesized in the skin and is sunlight-dependent, which poses an additional risk in the northern hemisphere. Dietary sources of vitamin D are limited. People with epilepsy (PWE) who are housebound or institutionalized, or have reduced physical activity, poor nutrition or avoid sunlight for cultural reasons, are at increased risk of deficiency and consequent bone disease. Associated conditions such as cerebral palsy and visual impairment may contribute to lower levels of physical activity. Hypovitaminosis D can cause a proximal myopathy with weakness and increased falls liability, whilst osteopenia/osteoporosis can render the person unsteady. Both myopathy and bone changes potentially increase the fragility fracture risk.

**1.1 Bone health and anti-seizure medication (ASM)**

Attention has also focused on ASM and its role in abnormal bone metabolism. A two-to-threefold increase in fracture risk has been associated in PWE with long-term use of ASMs. Whilst the relationship between abnormalities of bone health and ASMs is commonly thought to be due to the enzyme-inducing properties of many ASMs, leading to reduced serum vitamin D levels, this is not the only mechanism. Other mechanisms suggested including direct effects on bone cells, direct inhibition of intestinal calcium absorption, inhibition of osteoclast cell growth, inhibition of cellular response to parathyroid hormone and inhibition of calcitonin secretion.

**1.2 Bone health in intellectual disability (ID)**

A cross-sectional observational community study from Oxford UK in 2014 identified vitamin D deficiency, (defined as <50 nmol/L), in nearly twice as many people with ID in the community, compared with a control group from the general population. In the ID group, winter season, dark skin pigmentation, impaired mobility and obesity were independently associated with lower serum vitamin D levels.

Another study involving 100 people with ID in a secure inpatient service in the north of the UK in 2018, showed 83% had suboptimal vitamin D levels—deficiency was defined as <25 nmol/L and insufficiency as 25–49 nmol/L. There were no differences in terms of seasonality, antipsychotics, ASM or length of stay.

A 2010 literature review with a cross-sectional survey in the UK involving 149 people with ID identified an increased prevalence of the following osteoporosis risk factors: the use of ASMs (64%), immobility (23%), history of falls (20%) and fractures (11%). Just over half (54%) fulfilled the criteria for screening, and of those who then underwent DEXA scanning, 55% had osteoporosis and 33% had osteopenia. In their literature review, the authors found that most studies in individuals with ID identified two or more risk factors for reduced BMD. They concluded that there is a need for screening for risk factors associated with lower BMD in adults with ID. A cross-sectional study from the USA in 2008 of 298 individuals with ID, involving DEXA scanning, identified risk factors for osteoporosis of age, race and level of ambulation.

In a Canadian comparison study in 2017 comparing administrative data between individuals between the ages of 40 and 64, those with ID (30,522) were approximately three times more likely to experience a low-trauma fracture than those without ID (1,494,926). After a low-trauma fracture, there was no significant difference in the likelihood of receiving a BMD test between individuals in the two groups.

In a 2017 Irish national longitudinal study of older adults with ID as they age, 753 participants with varying levels of ID, aged 40 years and over, were randomly selected from a national ID database. The study showed 8.1% of participants reported a doctor’s diagnosis of osteoporosis with over 20% reporting a history of fracture. Older age, female gender and difficulty walking were found to be strong predictors for osteoporosis, whilst epilepsy and ASM were strong predictors for fractures. Overall, only 11.1% had bone screening diagnostics.

**1.3 Bone health in PWE and ID**

ASMs are frequently prescribed in people with ID. The recent England-based Learning Disability Mortality (death) Review (LeDeR) Report (2018–2021), which reviews yearly mortality of all individuals with ID in England revealed that 37% were being prescribed ASMs, at the time of their death. Three ASMs (valproate, carbamazepine and levetiracetam) were amongst the seven most common...
medications being prescribed. Epilepsy was the most common long-term health condition reported. The LeDeR Report also showed that people with ID were often on other medication, which could interfere with bone health.

A 2019 UK survey of service users and their carers receiving services from a specialist ID mental health Team found that there was little evidence that PWE and ID and/or their carers were informed about the risks that epilepsy and ASMs pose to bone health and the increased risk of fractures.14

2 | METHODOLOGY

This is a prospective observational study of clinical parameters related to bone health, in consecutive patients seen in a specialist community ID Epilepsy Clinic as part of their routine clinical follow-up, undertaken between 2015 and 2017. The STROBE guidance was used to guide this retrospective cohort study. The aims of the research were to identify the vitamin D status of patients with ID and epilepsy under the care of an UK urban ID community service and to enumerate the demographics, neurodevelopmental factors, biochemical markers of bone metabolism and bone mineral density (BMD), between patients with normal and low serum vitamin D levels. Seizure and/or epilepsy types were also classified into focal, generalized or mixed.

A local protocol was developed to aid clinicians to systematically screen for bone health and advise on treatment where appropriate. In view of the multiple comorbidities seen in individuals with ID, many of which are considered risk factors for poor bone health outcomes, and the authors had defined vitamin D insufficiency as 50–79 nmol/L, and deficiency as <50 nmol/L. Data were systematically collected and analysed to look for associations between serum vitamin D levels, BMD and other health and demographic factors.

In those patients with a vitamin D level <50 nmol/L a loading dose (vitamin D3 5000 IU daily for 8 weeks) followed by a maintenance dose of vitamin D (vitamin D3 2000 IU daily) was administered. In patients with a vitamin D level between 50 and 79 nmol/L, patients were commenced on the maintenance dose only. Vitamin D levels were rechecked 12 weeks after initiation of vitamin D replacement, and after every dose change. Post-vitamin D treatment average doses required for correcting deficiency and insufficiency in this population were calculated. The vitamin D prescribing was based on local guidance developed by consensus with the clinical team with the endocrinologist and no national set dosing protocol was used.

During the study period 2015 to 2017, serum vitamin D levels were measured using the Elecsys vitamin D total assay to quantitatively determine total 25-hydroxyvitamin D levels. The Elecsys Vitamin D total II assay is intended for the quantitative determination of total 25-hydroxyvitamin D in human serum and plasma. This assay is to be used as an aid in the assessment of vitamin D sufficiency in adults. PreciControl Vitamin D total II is used for quality control of the Elecsys Vitamin D total II assay. The manufacturer Roche Diagnostics Ltd technical data suggest that the coefficients of variation (CV) for PreciControl Varia 1to be 4.7% and Precicontrol Varia 2 to be 3.5%. The local laboratory’s own workup CVs were PreciControl Varia 1 at 8.1% and Precicontrol Varia 2 at 4.9%. BMD was measured using a GE-lunar Prodigy Dual-energy X-ray absorptiometry (DXA) scanner.

Ambulation status was defined as whether the participant was wheelchair dependent most hours of the waking day or not.

Data were collected from the patients’ clinical notes regarding current and previous exposure to ASMs and whether they had been exposed to enzyme inducers (carbamazepine, eslicarbazepine, phenobarbital, phenytoin and topiramate >200 mg/Di), non-enzyme inducers (clobazam, clonazepam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, sodium valproate and topiramate <200 mg/Di and Vigabatrin) or both.

2.1 | Patient recruitment

Patients were 18 years or older with established diagnoses of ID and Epilepsy, who were receiving ASM for a minimum of 2 years and were able to cooperate with blood tests and/or DEXA bone scanning. Exclusion criteria included patients who had psychogenic nonepileptic seizures only, and those with a diagnosis of epilepsy who had been on ASM for less than 2 years duration, or who could not cooperate with both blood tests and scanning.

2.2 | Data collection

Clinical data from the protocol were obtained using a standard clinical preform, which included the parameters shown in Table 1.

2.3 | Ethics

The project used anonymized pooled data from a single centre. Data were collected as part of ongoing service evaluation and registered as such respectively with the organization. The NHS Health research authority tool (http://www.hra-decisiontools.org.uk/research/index.html) confirmed no formal NHS Ethics approval was required (Appendix S1). No author had access to any patient identifiable information other than to the direct clinician (first author) within the service. The collected clinical data were stored anonymously on an EXCEL database and then shared for analysis.

2.4 | Analysis

Statistical analysis was performed on the data, using the Pearson correlation coefficient to assess the correlations between variables, and using t-tests where two groups were compared. The software used for analysis was RStudio Version 1.3.959.
3 | RESULTS

3.1 | Epilepsy and seizures

Of the cohort, 33 had focal onset seizures without secondary generalization (M = 21 F = 12), 36 had generalized seizures onset seizures only (M = 21 F = 15), and 35 had both focal and generalized onset seizures (M = 21 F = 14) (Table 2). The average years of epilepsy for the cohort were 29.44 years (range 5–63), for males 26.89 (range 5–63), and in females 30.61 (range 11–63). The number of years documented for each patient refers to the first mention of epilepsy in the case notes.

3.2 | Vitamin D levels

Of the eligible 104 patients in the service, 102 had a recorded vitamin D level. Results are shown in Figure 1. Of these, 76 (74.5%) patients were vitamin D deficient and 16 (15.7%) were vitamin D insufficient. A mean daily dose of vitamin D3 1264 IU was required to increase vitamin D serum levels above 80 nmol/L in those who were insufficient, and a mean dose of 2086 IU was required for those who were deficient. There was a significant increase in vitamin D levels after supplement for those who were deficient/insufficient at baseline (p < .001).

3.3 | Mean hip T-scores

Of the 104 patients, 76 (33 female and 43 male) were able to cooperate with a DEXA Bone Scan at baseline. Only a third (12 females, 14 males) had normal mean hip T-scores. Of the 41 females in the study cohort, 13 (17%) were osteopaenic and 8 (11%) were osteoporotic. Of the 63 males, 11 (14%) were osteopaenic and 18 (24%) osteoporotic. Only 5 patients were receiving Bisphosphonate therapy at baseline.

3.4 | Vitamin D levels, level of ID and ambulation

Vitamin D levels were low in all severities of ID. ID severity did not significantly impact serum vitamin D levels (Table S3). This was still true when controlled for ambulatory levels—the proportion of patients who were ambulant decreased with ID severity: 88.2%—mild, 72.0%—moderate and 31.1%—severe ID (Table S3).

3.5 | Vitamin D and calcium levels and DEXA hip T-score compared with alkaline phosphatase (ALP) levels

Patients with a high ALP had significantly lower baseline vitamin D levels than those with a normal ALP (p = .0027) (Figure 2). There was a borderline significant difference for calcium levels (p = .06) and no difference for DEXA hip T-scores (p = .2755) between those with a high and normal ALP.

3.6 | Vitamin D level and DEXA hip T-scores

DEXA hip T-scores were lower in patients with vitamin D deficiency/insufficiency compared with normal vitamin D; however, this was not a significant difference, p = .9393.
3.7 | DEXA hip T-score and ambulation

DEXA scores were significantly lower \( (p = .04618) \) in non-ambulant patients (Figure 3).

3.8 | DEXA hip T-scores and level of ID

DEXA hip T-scores (Table S3) appear to show a decreasing, non-significant, trend as ID severity increases (Figure 4). In all groups, the mean average DEXA hip T-scores were in the osteopaenic range.

3.9 | DEXA hip T-score compared with age

The mean average T-score was \(-1.705 (SD = 1.44, \text{range } -4.2 \text{ to } 1.8)\). Pearson’s correlation coefficient between the two variables was 0.012, indicating no correlation between age and DEXA hip T-score.

3.10 | Relationships between enzyme- and non-enzyme-inducing ASMs and bone parameters

Of the total sample for 92 people (male = 57 female = 35), the records were available of their epilepsy onset. Of these, 72 had exposure to enzyme-inducing ASMs of varying duration, concurrently or at some point in their past. Only 20 (males = 14 females = 6) had not been exposed to enzyme-inducing ASMs. Table S4 provides details of people exposed to enzyme-inducing ASMs and non-enzyme-inducing ASMs.

Vitamin D deficiency/insufficiency was significant in this population of people with ID and epilepsy. Only 10 patients of the 102 reviewed had normal baseline vitamin D levels. DEXA hip T-scores were lower for those with vitamin D deficiency/insufficiency at baseline. The mean DEXA T-score for this study was in the osteopenia range, regardless of age. Although this was non-significant, this may have been due to the small sample size. An approximate dose of vitamin D 1200 IU replacement was needed to correct vitamin D insufficiency and 2000 IU for deficiency.

3.11 | Other biochemical parameters

There were no significant abnormalities in calcium, inorganic phosphate, magnesium and parathyroid hormone levels.

4 | DISCUSSION

This is the first study done in England, which identifies and understands the characteristics of bone health status and the corrective nature of vitamin D in a whole adult cohort population of people with ID and epilepsy. The study provides unique perspectives of bone health status based on level of ID and ambulatory status, which can inform a more personalized approach to care. Only two patients were excluded from the study because of their inability to tolerate blood tests and DEXA scanning. Of the others, nearly three quarters successfully had a DEXA scan. The distribution of seizure types in our cohort is representative of this patient group as a whole.

Vitamin D deficiency/insufficiency was significant in this population of people with ID and epilepsy. Only 10 patients of the 102 reviewed had normal baseline vitamin D levels. DEXA hip T-scores were lower for those with vitamin D deficiency/insufficiency at baseline. The mean DEXA T-score for this study was in the osteopenia range, regardless of age. Although this was non-significant, this may have been due to the small sample size. An approximate dose of vitamin D 1200 IU replacement was needed to correct vitamin D insufficiency and 2000 IU for deficiency.
Nearly a quarter (22.12%) of patients had a high ALP level which was associated with a significantly lower vitamin D level. Routine laboratory ALP measurements usually include a combination of isoenzymes, mainly from the liver, bone and intestines. If liver function tests are otherwise normal, a raised ALP level is likely to be associated with low serum vitamin D levels and abnormal bone metabolism. Similarly, lower calcium levels appear to be associated with higher ALP and low vitamin D levels.

The percentage of ambulant patients decreased as ID severity increased. This may be due to presence of congenital handicaps or co-existing comorbidities such as cerebral palsy and other movement or genetic disorders influencing the ability to weight bear. DEXA hip T-scores were significantly lower in those who were non-ambulant suggesting that ambulance is an important signpost in indication of bone health status. The data also suggested a non-significant reduction in DEXA hip T-scores as ID severity increased.

As the duration of the epilepsy of the cohort is considerable, only around a fifth of the sample had no known exposure to non-enzyme-inducing ASMs. They generally were having seizures for less duration or younger in age. ASMs (enzyme inducers compared
with non-enzyme inducers) had no apparent impact on DEXA hip T-scores, PTH levels nor vitamin D levels. However, even in this small group, difference in ALP levels approached significance.

4.1 | Limitations

Seizure diagnosis was provided as generalized, focal without generalization and mixed types. This is simplistic representation, but it needs appreciation that it is difficult to diagnose seizure subtypes in people with ID. Furthermore, the focus of the paper is on the impact of seizures and its medication; thus, the seizure type itself is not the main issue of study. It was also obvious for some patients that they would probably suffered from epilepsy for much longer—for example from infancy/childhood, but the age of onset simply was not recorded in the clinical notes.

Of the 104 patients, 13 had dark skin, which is consistent with Black, Asian and Minority Ethnic groups comprising 15.68% of the total local population. Meaningful comparisons could not be performed in this study due to the small sample. Vitamin D levels were measured at different times of the year and the amount of sunlight exposure was not measured or estimated, which will have had an impact on serum vitamin D levels.

Many of the patients received multiple enzyme-inducing ASMs either in succession or contemporaneously. This left only 20 patients unexposed to enzyme-inducing ASMs, which reduced the power of comparisons between those exposed or not exposed to enzyme-inducing ASMs. Also, since clinical notes were incomplete in addressing the duration of treatment and/or doses of ASMs, it was not possible to establish whether either of these factors make a contribution to bone health.

It is also well recognized that many other factors, including genetics, and other medication particularly psychotropics contribute to BMD. Furthermore, the focus has been on core bone health factors and core seizure issues such as dosage and type of ASMs (including whether enzyme-inducing, or not), and other metabolic parameters such as vitamin B12 levels, socio-cultural habits eg alcohol intake, and diet have not been inquired into. However, this study was a pragmatic real-world initiative, which identifies insights to recognize and treat worsening factors influencing bone damage in the long term.

4.2 | Implications for clinical practice

It is clear from the current study that people with ID and epilepsy are at very high risk for bone-linked harm compared not only with the general population but also with the specific populations of people with ID or epilepsy respectively. A 2009 study conducted in institutionalized adults with ID in Finland found that vitamin D insufficiency was common and that with a daily dosing of vitamin D 800 IU, the recommended level (>80 nmol/L) was attained in 42%. The authors recommended vitamin D supplementation with an oral dose of 800 IU per day to all adults with ID living in nursing homes. This study is in keeping with our findings. In our study population, larger doses of vitamin D were required to correct the deficiency. It might be that regular vitamin D supplementation in this vulnerable population reduces the risk of deficiency.

There is a case clinically to monitor this high-risk group from very early on in their life using bone-linked parameters such as vitamin D, ALP, calcium and BMD (using DEXA scan). It is important to recognize the practicalities of doing this with a population, which can be resistive to be actively investigated due to lack of cognitive abilities to process the need. It thus needs to be an active and regular consideration. There might even be a case to consider treating high-risk patients with vitamin D supplementation in their best interest based on perceived clinical risk.

In a literature review of bone health in PWE and treated with ASM in 2018, PWE were considered as being at increased risk of bone disease, as evidenced by changes in bone turnover, osteoporosis, alterations in bone quality and fractures. Biochemical indices of bone metabolism included calcium, vitamin D and parathyroid hormone. Whilst no single mechanism explains all the changes associated with epilepsy and ASM, the authors recommended BMD screening for persons with long-term ASM exposure particularly if they had other risk factors for bone disease.

A greater awareness of the multiple risk factors for hypovitaminosis D and reduced BMD within this cohort should lead to baseline vitamin D measurements and DEXA scanning or a suitable alternative, for example quantitative ultrasound measurements (QUS), if the patient cannot cooperate, and commencing corrective vitamin D where appropriate.

The use of QUS has been subject to some debate. An observational cross-sectional study from Republic of Ireland from health assessments done between 2013 and 2016 used data of QUS, to evaluate skeletal health in 575 participants with ID aged 43 years and over. QUS identified osteopenia in 33.2% and osteoporosis in 41% of the sample. The authors acknowledged that whilst QUS was not the gold standard for measurement of BMD, it did comply with the standards and position defined by the International Society of Clinical Densitometry and highlighted the considerable burden of...
poor bone health in the ID populations. Furthermore, it can be argued that if the patient is un-co-operative to avail DEXA scanning as is not uncommon in people with ID, then QUS might be a reasonable alternative.

4.3 | Implications for research

A recent study demonstrated increases in BMD in patients on long-term vitamin D supplementation, who had previously been vitamin D deficient. Such situations will require further research and study. There is lack of specific guidance for GPs, pharmacists and epileptologists regarding management for this vulnerable cohort, and a need for a standardized protocol/checklist for identifying and modifying risk factors to optimize the bone health in PWE and ID. Such a protocol could evolve into patient/carer literature (including easy read materials) on wider strategies to improve bone health.

The role of vitamin D in bone mineralization and skeletal maintenance is well established. However, the discovery of vitamin D receptors in various tissues suggests that it has functions in other diseases. Ensuring that PWE and ID have optimal serum vitamin D levels are likely to have benefits in a range of conditions, beyond osteopenia/osteoporosis, and vitamin D possibly needs proactive recommending for vulnerable groups. These issues need further inquiry.

There is also a risk of more people with ID being prescribed ASMs as psychotropic medicines, as clinicians change their prescribing practice secondary to reducing the overuse of antipsychotic medication in the ID population for behavioural management. Whilst ASMs can have some positive benefit on behavioural issues, long-term impact especially on issues such as bone health has not been studied.

An area which needs further exploration is the dosing and efficacy of vitamin D tailored to enzyme-inducing ASMs versus non-enzyme-inducing. There is developing evidence suggestive of enzyme-inducing ASMs reducing the effectiveness of vitamin D.

5 | CONCLUSION

This study looks to open the narrative of diagnosing and managing bone health in a vulnerable, often neglected and hard to access population. It outlines potential areas of easy prevention, that is use of vitamin D which might help retard or stop bone damage.

People with epilepsy and ID remain a vulnerable population for adverse health outcomes and premature mortality due to multitude of reasons. Insights into the challenges of supporting this vulnerable group are at its infancy. The status of bone health is a likely bellwether to the bigger picture of well-being in this vulnerable population. Thus, when managing a person with ID with epilepsy, it is important to ‘think bone’.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All substantially contributed to the design, analysis, interpretation of the work, drafting and preparation of the manuscript, final approval of the manuscript and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work. All authors meet all four ICMJE criteria for authorship.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author.

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**SUPPORTING INFORMATION**
Additional supporting information may be found in the online version of the article at the publisher’s website.

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