DR ANNE TRINH (Orcid ID : 0000-0003-4990-8784)

Article type : 3 Original Article - Australia, Japan, SE Asia

Longitudinal changes in bone density in adolescents and young adults with cerebral palsy: a case for early intervention

Running title: Longitudinal changes in bone density in cerebral palsy

Trinh, Anne ^{1,2,3}, Wong, Phillip ^{1,2}, Fahey, Michael C ^{2,4}, Brown, Justin ^{4,5}, Strauss, Boyd J³, Ebeling, Peter R ^{1,3}, Fuller, Peter J ^{1,2}, Milat, Frances ^{1,2,3}

¹ Department of Endocrinology, Monash Health, Melbourne, Australia

² Hudson Institute of Medical Research, Clayton, Melbourne, Australia

³ Department of Medicine, Monash University, Melbourne, Australia

⁴ Department of Paediatrics, Monash Health, Melbourne, Australia

⁵ Department of Paediatric Endocrinology and Diabetes, Monash Health, Melbourne, Australia

Corresponding author and person to whom reprints should be addressed:

Dr Anne Trinh, Department of Endocrinology, Monash Health, 246 Clayton Rd Clayton 3168, Victoria Australia. Email: anne.trinh@monash.edu

Acknowledgements

This research is supported by a Cerebral Palsy Alliance Research Foundation Grant. AT is supported by a Research Training Program scholarship from the Australian Government. FM is supported by an Endocrine Society of Australia Ken Wynne Post-Doctoral Grant. PW is supported by an NHMRC Early Career Fellowship. The Hudson Institute is supported by the Victorian Government's

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/CEN.14052](https://doi.org/10.1111/CEN.14052)

Operational Infrastructure Support program.

Key words: cerebral palsy, bone density, longitudinal, puberty

Data availability statement: The data that support the findings of this study are available from the corresponding author, AT, upon reasonable request.

Conflict of interest statement: The authors have no conflicts of interest to declare

Abstract

Context: Cerebral palsy (CP) is a motor disorder affecting movement, muscle tone and posture due to damage to the fetal or infant brain. The subsequent lack of ambulation, nutritional deficiencies, anticonvulsant use and hormonal deficiencies have been implicated in the low bone mass associated with this condition.

Objective: To assess changes in areal bone mineral density (aBMD) during adolescence and young adulthood in individuals with CP. The effect of ambulation, nutrition, hypogonadism on longitudinal changes in aBMD is also examined.

Design: Retrospective longitudinal study

Setting and participants: Forty-five subjects with CP who had longitudinal dual-energy x-ray absorptiometry (DXA) scans at a single tertiary hospital between 2006 and 2018.

Results: Mean age at first DXA was 19.4 years (range: 10 - 36 years), 57.8% were male and 80% were non-ambulatory. The mean Z-scores at baseline were <-2.0 at all sites - lumbar spine (LS), femoral neck (FN), total hip (TH) and total body (TB). The median change in aBMD was +1.2-1.9%/year in all subjects but in those <20 years of age, the median change was 4-8%/year. Z-scores across all sites remained stable over time. Reduced functional state as measured by the gross motor functional classification scale (GMFCS) had a small negative effect on aBMD over time.

Conclusion: In adolescents with CP, low bone mass was evident from the baseline DXA. However, significant bone accrual occurred during the second decade, followed by bone maintenance in young adulthood. Future studies should focus on optimising bone health from early childhood.

Key words: cerebral palsy, osteoporosis, fracture, longitudinal, bone density

Introduction

Cerebral palsy (CP) is the most common motor disorder among children, resulting from a static insult to the developing fetal or infant brain. As CP life expectancy continues to improve ¹, there is increasing recognition that a lifespan approach is needed to maintain both health and function. As these individuals age, many become dependent on assistive devices ² and up to 75% of individuals lose their ability to mobilise ³. Preserving bone and muscle health to maintain mobility and independence is therefore critical.

Adults with CP are particularly vulnerable to osteoporosis and fracture due to their longer cumulative exposure to risk factors that lead to bone loss and declining bone mass with age ⁴. In a large cohort of 435 adults aged 40-60yo with CP in Michigan, up to 58% of adults with Gross Motor Function Classification Scale (GMFCS) IV-V and 40% with GMFCS I-III had documented osteopenia/osteoporosis ⁵. In a small study of predominantly non-ambulatory adults with CP, prevalent fractures were present in 38%, with 53% of fractures occurring in adulthood ⁶. However, it is unclear whether low bone mass in adults with CP is predominantly due to less bone accrual during childhood, earlier onset of bone loss or an accelerated rate of bone loss in adulthood compared with the general population.

In recent years, small cross-sectional studies in adults with CP have demonstrated the importance of ambulation on bone mineral density (BMD) as measured by dual x-ray absorptiometry (DXA) ⁷⁻⁹. Other factors associated with low BMD in these studies included type of CP (dyskinetic vs spastic), low BMI, presence of hypogonadism and decreased lean mass ^{6-8,10}.

Small longitudinal studies of bone density in CP have inconsistent findings. In 69 children with CP aged 2 to 17 years (followed for 2-4 years), an increase in BMD of 2% per year at the distal femur and 5% per year at the lumbar spine was shown but distal femur Z-scores decreased with age ¹¹. This suggests that the rate of bone accrual in CP was less than typically developed children. In a cohort of 40 subjects with CP aged 6 to 26 years (followed for up to 6 years), the yearly change in distal femur BMD was 0.7%-1.0% and was positively correlated with weight ¹². However, in both studies, it was noted that the yearly changes in BMD varied widely between -31% to 42%. This is likely to be secondary to positioning difficulties in the presence of contractures and motion artefact. In a study of 15 predominantly non-ambulatory adults, using lumbar spine and femoral neck as the region of interest, there were non-significant declines in BMD and BMD Z-scores over time ⁹.

In view of the lack of studies of longitudinal bone density in adolescents and young adults with CP, the aim of this study was to assess bone accrual in the second decade of life and the changes in BMD in adulthood. We also investigated the effect of ambulation, functional state, nutrition, hypogonadism and weight on BMD longitudinally.

Methods

Subjects.

Monash Health is a tertiary hospital in Victoria, Australia that provides care across the lifespan with obstetric, newborn, paediatric and adult services. Children with CP are seen in specialist medical clinics and the Victorian Paediatric Rehabilitation Service (VPRS). As an adolescent, they are linked into the Young Adults Transition Clinic which takes referrals state-wide, and then referred on to adult services. One such service is the Metabolic Bone Clinic at Monash Health, which is staffed by both paediatric and adult endocrinologists to allow the smooth transition of care of these patients; it is uniquely placed to understand longitudinal changes in bone health this group.

A retrospective longitudinal analysis of 45 individuals with CP who had more than one DXA study from 2006-March 2018 was performed. Individuals had DXA imaging for suspected low BMD in the setting of immobility, fracture, anticonvulsant use or hypogonadism. Routine practice in the clinic was to order repeat scans every 1 to 2 years; individuals did not have repeat scans only if they declined or were lost to follow-up. Subjects were included if they were 10 years of age or older during their first DXA scan in order to assess changes in BMD in the second decade. This cut-off was based on the lower end of the normal range of pubertal onset in North America and Europe, which is 8 years in girls and 9 years in boys¹³. The study was approved by the institutional ethics committee (Monash Health HREC).

BMD measurements

Bone quantity was measured as bone mass in grams per anterior posterior projected area of measured bone in cm squared or areal BMD (aBMD), not true bone density. Sites of measurement by DXA included lumbar spine (L2-L4), proximal hip and total body (including head) on all participants unless limited by previous scoliosis surgery, femoral surgery or difficulty positioning the subject. Subjects were scanned from L1-L4 in all cases. However, when scans were reviewed individually, in subjects with scoliosis, L1 was often involved in the inflection of the curve making it difficult to reproduce reliable measurements between scans. L2-4 was therefore chosen for analysis. The majority of scans were performed by one technician, and were given 1 hour timeslots to allow for positioning difficulties and the need to acquire multiple scans if motion artefact was present. One researcher (AT) assessed all scans to determine whether there was significant motion artefact or large variations in the region of interest and excluded these sites from analysis.

All measurements were obtained using a GE Lunar Prodigy (Madison, Wisconsin) and retrospectively analysed with one software version (version 17) at a single centre. Anthropometric measures of age, weight and height were documented. In cases where true height could not be obtained, length while

lying flat was used. In those aged <20 years, gender and age specific height Z-scores were calculated using the Centre for Disease Control (CDC) 2000 growth charts.

Low BMD was pre-specified and defined as a Z score of ≤ -2.0 as per the International Society of Clinical Densitometry guidelines for adults < 50 years of age¹⁴. The coefficient of variation (CV) for BMD on our DXA using an Hologic anthropomorphic lumbar spine phantom measured daily over the period from 2004-2011 was 0.51%.

Data collection and clinical measures

GMFCS grades the severity of gross motor function impairments based on the ability to mobilise or need for assistive devices¹⁵. Levels range from I to V with individuals at level V having the greatest impairment and are wheelchair bound. GMFCS was obtained from the medical records, and participants divided into two groups: predominantly ambulatory (GMFCS I-III) or non-ambulatory (GMFCS IV-V).

A history of gonadal dysfunction including delayed puberty was established from the medical record. Hypogonadism was defined in males as the use of androgen replacement therapy or low testosterone levels ($<8\text{nmol/L}$) documented on two separate occasions; and in females as the use of hormone replacement therapy, menopause before the age of 40 or low oestradiol levels ($<73\text{pmol/L}$) on two separate occasions. Where possible, timing of puberty, age of menarche and bone age was documented. Bone age was estimated from a hand x-ray using the Greulich and Pyle (GP) method. Delayed puberty was defined as the absence of testicular enlargement in boys or breast development in girls at an age that is more than 2 standard deviations later than the population mean (age of 14 years in boys and 13 years in girls).

Current or past use of anticonvulsant medication and use of percutaneous endoscopic gastrostomy (PEG) feeding was obtained from the medical record. Minimal trauma fracture was defined as either a self-reported or radiologically proven fracture occurring after a fall from standing height or less, or a minimal trauma incident other than a fall (e.g. turning over in bed). Bisphosphonate use was defined as any exposure to bisphosphonate prior to first DXA or during follow-up. Vitamin D levels that were done within 6 months of DXA were collected.

Statistical analysis

The distribution of the data was explored by the Shapiro-Wilk test. All normally distributed data were expressed as mean with standard deviation and non-parametric data as median with interquartile ranges. Univariate analysis was used to determine the relationship between variables and baseline aBMD. Mixed model analyses was used to determine the significance of changes in aBMD and Z-score over time, with time defined as the number of years since baseline DXA. All models were

analysed as random intercept with time as a fixed variable. The effect of variables on longitudinal changes in aBMD was calculated and reported as parameter estimates. Subjects were divided into <20 years old and ≥ 20 years old to assess for differences in changes in BMD and Z-score, as the rapid increases in BMD seen in puberty should have largely occurred by age 20¹⁶. Subjects who had measurements that fell into both categories were included in one age category only and the other measurements were excluded. Independent samples t-test was used to compare baseline aBMD and Z-scores between those aged <20 years and those ≥ 20 years, and chi square used for categorical variables. Mann Whitney U test was used to compare annualised median change in aBMD and Z-score between those aged <20 years and those ≥ 20 years. A two-sided p-value of 0.05 was chosen to indicate statistical significance. Analyses were conducted using IBM SPSS Statistics for Windows (Version 24, Armonk, NY).

Results

Forty-five patients with cerebral palsy who had more than one DXA scan were included in the study. 30 patients (66.7%) had more than two scans for analysis, whilst 16 patients (35.6%) had five or more scans for analysis. 50% of patients had at least 4 years of follow-up, with the mean interval between scans 1.6 ± 1.1 years. Baseline characteristics of the patients and baseline DXA-derived aBMD and Z-scores are shown in Table 1. Mean age (range) at first DXA was 19.4 years (10 - 36), 12 patients (26.7%) were less than 20 years old at their first DXA scan. For subjects aged <20 years at their first DXA, the mean age of initial DXA was 13.9 ± 3.1 years. 57.8% were male and 80% were non-ambulatory. Anticonvulsant use was common (n=27, 60%), most (n=20) were on multiple agents with the most common agents being sodium valproate, lamotrigine and carbamazepine. Apart from three patients, there was a long duration of anticonvulsant use of >10 years as seizures presented shortly after birth or developed in childhood. Mean BMI of subjects was 18.3 ± 4.5 kg/m² and 31.1% required PEG feeding. Minimal trauma fracture was documented in 42.2% of subjects, the majority of these (76.2%) involved the femur or tibia/fibula.

Fifteen subjects (33.3%) were hypogonadal; 9 were female. All female patients had a history of delayed puberty; mean age of menarche for these patients was 18 ± 3 years. Of the 6 male patients with hypogonadism, 2 presented with delayed puberty and the remainder developed hypogonadism as an adult. Overall, 9 of the 15 patients received hormone induction/hormone replacement therapy.

Eleven subjects (24.4%) received bisphosphonates, one patient received bisphosphonate for avascular necrosis while the remainder received bisphosphonates for osteoporosis and fracture. All patients received zoledronic acid, one patient initially received pamidronate followed by zoledronic acid. Doses of zoledronic acid were 4-5mg intravenously if given to adult patients, and doses in children

were weight-adjusted (0.05mg/kg). The number of doses and dosing interval varied upon the clinical situation; adults were given between 1-4 doses of zoledronic acid at 12 monthly to 24-monthly intervals whereas children were given a total of 2-6 doses of intravenous zoledronic acid at 6 monthly intervals. Vitamin D3 was supplemented to aim for serum levels >50nmol/L and often involved the use of high dose intermittent dosing (typically 50,000IU/dose) for convenience.

At first baseline scan, mean Z-scores at the lumbar spine (LS), femoral neck (FN), total hip (TH) and total body (TB) were all ≤ -2.0 . Subjects who were aged <20 years at baseline scan had a trend to a lower FN and TH Z-score than those aged ≥ 20 years at baseline scan, but this did not reach statistical significance (Table 1). Bone age x-ray was performed in 10 of the 12 subjects aged <20 years, with a mean delay in bone age of 1.1 ± 1.6 years. Mean age and gender specific height Z-score in those aged <20 years was -1.7 ± 1.4 . There was no significant change in height Z-score per year (0.15/year, 95% CI -0.02 to 0.31, $p=0.084$). In those aged ≥ 20 years, mean height was for females was 144.5 ± 5.5 cm and for males was 161.0 ± 13.5 cm.

Total body bone mineral content (TBBMC), LS aBMD, and FN aBMD, TH aBMD was plotted against the age of the patient to gain an approximation of when peak bone mass was achieved (see Figure 1). Linear, cubic and quadratic line of best fit was calculated and the line with the greatest R^2 was chosen ($R^2=0.330$, $p=0.02$). Peak bone mass appeared to be achieved late in the third decade of life/early in the fourth decade and plateaued thereafter. FN aBMD appeared to peak earlier than LS aBMD (Figure 1B and 1D).

TBBMC, aBMD and Z-score at the LS, total hip (TH), and total body (TB) increased slightly in the overall analysis and was statistically significant (Table 2). There were wide variations in changes in aBMD ranging between losses of -22% and gains of +38% per year. Subjects were then divided into those aged <20 years and ≥ 20 years. At baseline, the only difference in clinical variables between the two age groups was BMI (<20 years mean BMI 15.8 ± 3.1 kg/m² vs ≥ 20 years 19.2 ± 4.6 kg/m², $P=0.019$) (see Table 1). There was a significant difference in the change in TBBMC and aBMD per year between the two groups, with those aged <20 years having a 4-8% increase in aBMD per year compared with minimal changes in aBMD in those aged ≥ 20 years (Table 3). Bisphosphonate exposure was similar in both groups, 28.6% in those <20y vs 27.3% in those ≥ 20 y, $p=0.927$ and this did not have a significant impact on changes in Z-scores over time in either age group.

The effect of sex, ambulatory status and functional status, hypogonadism, bisphosphonate use and weight on change in aBMD and TBBMC over time was assessed using mixed model analysis (Table 4). Reduced functional status as measured by GMFCS had a negative effect on aBMD of the order of -0.01g/cm²/year at the LS, TH and TB ($p<0.01$). There was a statistically significant effect of vitamin D and weight on change in aBMD at all sites, although the magnitude of change was clinically unimportant being 0.001-0.0001g/cm²/year. Females had a greater increase in aBMD at most sites

compared with males, by 0.007-0.011g/cm²/year (p<0.05). The other assessed variables had an inconsistent or non-significant effect on changes in aBMD and TBBMC over time. A subgroup analysis was performed in subjects aged <20 years and ≥20 years of age which did not demonstrate a clinically significant association between any variables with aBMD or TBBMC.

Discussion

In our study, adolescents with CP gain aBMD during puberty with a median increase of 4-8% per year, followed by a period of consolidation in young adulthood. This finding is in keeping with longitudinal data from typically developing children in the second decade of life and is reflected in the stability of Z-scores over time. Our observed change in aBMD/year is comparable to that seen by Henderson *et al.*¹¹, who found a 5.0-6.4% mean change in aBMD/year in their 12-19 year old group. A key strength of our study is that we had repeated measurements in the same subject. aBMD is challenging to obtain in this population due to contractures, scoliosis and movement artefact. Technically, this is reflected in the wide variation in aBMD between two scans (ranging from -22 to +38%) in our study, as was also observed in other longitudinal studies. As a result of these variations, repeated measurements allowed the recognition of these inconsistencies in aBMD over time. In our clinical experience, given these disparities, we do not base treatment decisions in this cohort on the change in aBMD between two scans but rely on the overall trend.

By choosing the lumbar spine and proximal hip as sites of measurement, we could calculate Z-scores for this cohort. Of note, the mean baseline Z-scores at all sites measured were <-2.0, suggesting that the deficit in bone mass had occurred in the first decade of life. In those <20 years, even after taking into consideration mean height Z-scores of -1.7±1.4, mean Z-scores of -3.6 at the FN and -3.7 at the LS are concerning. Height Z-score did not change significantly over time, suggesting that growth failure occurs earlier in childhood. This is consistent with cerebral palsy specific growth charts which show linear growth failure present from age 2, with only slight worsening over time¹⁷.

It is reassuring that aBMD Z-scores are stable over time, suggesting bone accrual and maintenance occur in parallel to typically developing adolescents albeit at a lower set-point. This result requires validation as it is in contrast to the findings of Henderson *et al.*¹¹ which showed that Z-scores declined at the distal femur over time but increased at the lumbar spine. Possible explanations may be that their cohort included younger children from the age of 2 years, as well as difference in the DXA sites measured. The lateral distal femur may be preferred over the proximal hip in childhood CP and other neurodisabilities¹⁸, with improved positioning in the setting of metallic hip implants and

contractures, and validation against fracture outcomes¹⁹. However, reference data is only available for Hologic scanners, and there is no adult normative data to allow for calculation of Z-scores. Therefore, measurements of the proximal femur should be considered in adolescence to allow monitoring through to adulthood.

We postulate given the stability of Z-scores in our cohort, deficits in bone accrual earlier in life rather than bone loss in adolescence or early adulthood is the predominant cause of low bone mass in adults with CP. Treatments to optimise bone health in CP need to be tailored to this new understanding. To determine the optimal timing of intervention, we estimated peak bone mass in CP by plotting BMC and aBMD as a function of patient age. Peak bone mass in this cohort of individuals with CP occurred in the late third/early fourth decade of life, with aBMD at the femoral neck peaking earlier than the lumbar spine. The Canadian CaMOS study revealed similar findings although at an earlier age, with aBMD at the femoral neck peaking at ages 16-19 in females and 19-21 in males, whereas lumbar spine aBMD peaked at ages 33-40 in females and 19-33 in males²⁰. This difference may be due to the high rates of delayed puberty and subsequent delayed bone accrual in our cohort. Early intervention in childhood to improve nutrition and mobility or use of pharmacological therapy may be crucial in the prevention of low bone mass and fractures in adulthood. Timely pubertal induction is likely to be important to optimise bone health into adulthood. Bisphosphonates produce much larger changes in aBMD and BMC in children compared with adults; consideration as to whether to administer bisphosphonates earlier in CP is an important clinical question. Current guidelines suggest that bisphosphonates be given in children with CP in the presence of either a vertebral fracture, or Z-score ≤ -2.0 and 2 or more long bone fractures²¹.

Reduced functional status as measured by GMFCS had a small negative effect on change in aBMD over time in our cohort of $-0.01\text{g/cm}^2/\text{year}$. It was surprising that functional status as measured by GMFCS or ambulation status did not have a greater effect as cross-sectional studies in both children and adults with CP have shown a consistent positive effect of ambulation on aBMD. By excluding subjects <10 years of age, we may not have captured the impact of ambulation on bone accrual given the onset of motor deficits in CP at birth. Unfortunately, we had insufficient numbers to assess how the loss of ambulation affects aBMD. Only one subject in our cohort went from walking daily with a frame to being a wheelchair user; other patients who had a change in mobility status went from using a standing frame to non-weight bearing.

We were unable to find any other variables that had a significant effect on changes in BMD over time in mixed model analyses. Bisphosphonate use did not appear to affect aBMD; this is surprising but may be partly explained by the variability in the age of the patient when the medication was given, the type of bisphosphonate administered, the dose administered and the duration of treatment. Furthermore, the variations in aBMD year to year of a given subject may mask any effect of

bisphosphonate on aBMD. Treatment of hypogonadism was inconsistent, and so the real effect of sex-steroid deficiency on bone accrual could not be ascertained. Baseline BMI for our cohort was $18.3 \pm 4.5 \text{ kg/m}^2$ with those <20 yrs having a mean BMI of only $15.8 \pm 3.1 \text{ kg/m}^2$. This is likely to be an important risk factor for low bone mineral accrual due to the consequences of reduced load bearing, nutritional deficiencies and effects on gonadal function. This was not borne out by our longitudinal findings, with no correlation between weight and BMD in either the <20 or >20 year old groups.

The main limitation of our study is the small number of patients and the lack of control group for our study cohort. Our study subjects already had risk factors for low BMD and does not represent the CP population as a whole. 72% of our cohort had a GMFCS level of IV or V whereas 34% of a birth cohort of Victorian CP cases obtained through a statewide register between 1990-1992 had a GMFCS of IV or V²². There were insufficient measurements in adults >30 yrs to determine when adults with CP begin to lose bone. The heterogeneity in duration of follow-up may also affect our estimation of peak bone mass. The wide variations in changes in aBMD per year reduce the certainty of our observations and may explain the lack of variables associated with longitudinal changes in aBMD in our cohort. This reflects the problems of DXA scanning in CP. However, no viable, readily available alternative quantitative technique to assess BMD exists at present. We are reassured that our findings are similar to the previous work in this field. The Australian BMD reference range for the Lunar Prodigy was derived from different cohorts for those <20 years to those ≥ 20 years which may affect comparisons between the two groups.

An inherent limitation of using DXA is that it does not measure true volumetric bone density (vBMD). aBMD will increase during growth predominantly due to increases in size rather than true density. For example, as the size of the vertebral body increases during growth, the amount of bone within it (BMC) also increases so vBMD remains the same although aBMD increases²³. DXA BMC may therefore be superior to DXA aBMD for assessing bone mass accrual in children²⁴. Volumetric bone density measurements would be advantageous but these can be difficult to obtain in this population, as they are particularly susceptible to movement artefact. We have therefore also reported Z-scores and BMC values to try and address these issues of size and growth.

In conclusion, deficits in bone mass in CP are seen before puberty. Individuals with CP still have significant bone accrual during pubertal years with a median increase of 4-8% in aBMD per year. The low bone mass seen in adults with CP is likely a reflection of poor bone accrual in early childhood rather than being due to rapid bone loss. Interventions during childhood such as improving muscle strength and mobility, optimising nutritional and hormonal status, and judicious use of bisphosphonates are likely key to achieving optimal adult bone health.

Conflict of interest statement: The authors have no conflicts of interest to declare

328   **References**

- 329   **1.**   Hemming K, Hutton JL, Pharoah PO. Long-term survival for a cohort of adults with cerebral
330   palsy. *Developmental medicine and child neurology*. Feb 2006;48(2):90-95.
- 331   **2.**   Bottos M, Feliciangeli A, Sciuto L, Gericke C, Vianello A. Functional status of adults with
332   cerebral palsy and implications for treatment of children. *Developmental medicine and child*
333   *neurology*. Aug 2001;43(8):516-528.
- 334   **3.**   Murphy KP, Molnar GE, Lankasky K. Employment and social issues in adults with cerebral
335   palsy. *Archives of physical medicine and rehabilitation*. Jun 2000;81(6):807-811.
- 336   **4.**   Sheridan KJ. Osteoporosis in adults with cerebral palsy. *Developmental medicine and child*
337   *neurology*. Oct 2009;51 Suppl 4:38-51.
- 338   **5.**   Cremer N, Hurvitz EA, Peterson MD. Multimorbidity in Middle-Aged Adults with Cerebral
339   Palsy. *Am J Med*. Jun 2017;130(6):744 e749-744 e715.
- 340   **6.**   Trinh A, Wong P, Fahey MC, et al. Musculoskeletal and Endocrine Health in Adults With
341   Cerebral Palsy: New Opportunities for Intervention. *The Journal of clinical endocrinology*
342   *and metabolism*. Mar 2016;101(3):1190-1197.
- 343   **7.**   Fowler EG, Rao S, Nattiv A, Heberer K, Oppenheim WL. Bone Density in Premenopausal
344   Women and Men Under 50 Years of Age With Cerebral Palsy. *Archives of physical medicine*
345   *and rehabilitation*. Jul 2015;96(7):1304-1309.
- 346   **8.**   Yoon YK, Kim AR, Kim OY, Lee K, Suh YJ, Cho SR. Factors affecting bone mineral density
347   in adults with cerebral palsy. *Ann Rehabil Med*. Dec 2012;36(6):770-775.
- 348   **9.**   Marciniak C, Gabet J, Lee J, Ma M, Brander K, Wysocki N. Osteoporosis in adults with
349   cerebral palsy: feasibility of DXA screening and risk factors for low bone density.
350   *Osteoporosis international : a journal established as result of cooperation between the*
351   *European Foundation for Osteoporosis and the National Osteoporosis Foundation of the*
352   *USA*. Apr 2016;27(4):1477-1484.
- 353   **10.**   Kim W, Lee SJ, Yoon YK, Shin YK, Cho SR, Rhee Y. Adults with spastic cerebral palsy
354   have lower bone mass than those with dyskinetic cerebral palsy. *Bone*. Feb 2015;71:89-93.
- 355   **11.**   Henderson RC, Kairalla JA, Barrington JW, Abbas A, Stevenson RD. Longitudinal changes
356   in bone density in children and adolescents with moderate to severe cerebral palsy. *The*
357   *Journal of pediatrics*. Jun 2005;146(6):769-775.
- 358   **12.**   Grossberg R, Blackford MG, Kecskemethy HH, Henderson R, Reed MD. Longitudinal
359   assessment of bone growth and development in a facility-based population of young adults
360   with cerebral palsy. *Developmental medicine and child neurology*. Nov 2015;57(11):1064-
361   1069.
- 362   **13.**   Carel JC, Leger J. Clinical practice. Precocious puberty. *N Engl J Med*. May 29
363   2008;358(22):2366-2377.

- 364 14. Adult Official Positions of the International Society of Clinical Densitometry 2015.
365 <https://iscd.app.box.com/OP-ISCDC-2015-Adult-Eng>.
- 366 15. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and
367 reliability of a system to classify gross motor function in children with cerebral palsy.
368 *Developmental medicine and child neurology*. Apr 1997;39(4):214-223.
- 369 16. Modlesky CM, Whitney DG, Singh H, Barbe MF, Kirby JT, Miller F. Underdevelopment of
370 trabecular bone microarchitecture in the distal femur of nonambulatory children with cerebral
371 palsy becomes more pronounced with distance from the growth plate. *Osteoporosis*
372 *international : a journal established as result of cooperation between the European*
373 *Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. Feb
374 2015;26(2):505-512.
- 375 17. Wright CM, Reynolds L, Ingram E, Cole TJ, Brooks J. Validation of US cerebral palsy
376 growth charts using a UK cohort. *Developmental medicine and child neurology*. Sep
377 2017;59(9):933-938.
- 378 18. Crabtree NJ, Arabi A, Bachrach LK, et al. Dual-energy X-ray absorptiometry interpretation
379 and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions.
380 *Journal of clinical densitometry : the official journal of the International Society for Clinical*
381 *Densitometry*. Apr-Jun 2014;17(2):225-242.
- 382 19. Henderson RC, Berglund LM, May R, et al. The relationship between fractures and DXA
383 measures of BMD in the distal femur of children and adolescents with cerebral palsy or
384 muscular dystrophy. *Journal of bone and mineral research : the official journal of the*
385 *American Society for Bone and Mineral Research*. Mar 2010;25(3):520-526.
- 386 20. Berger C, Goltzman D, Langsetmo L, et al. Peak bone mass from longitudinal data:
387 implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. *Journal of*
388 *bone and mineral research : the official journal of the American Society for Bone and*
389 *Mineral Research*. Sep 2010;25(9):1948-1957.
- 390 21. Modlesky CM, Kanoff SA, Johnson DL, Subramanian P, Miller F. Evaluation of the femoral
391 midshaft in children with cerebral palsy using magnetic resonance imaging. *Osteoporosis*
392 *international : a journal established as result of cooperation between the European*
393 *Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. Apr
394 2009;20(4):609-615.
- 395 22. Howard J, Soo B, Graham HK, et al. Cerebral palsy in Victoria: motor types, topography and
396 gross motor function. *Journal of paediatrics and child health*. Sep-Oct 2005;41(9-10):479-
397 483.
- 398 23. Ott SM, O'Hanlan M, Lipkin EW, Newell-Morris L. Evaluation of vertebral volumetric vs.
399 areal bone mineral density during growth. *Bone*. Jun 1997;20(6):553-556.

24. Wren TA, Liu X, Pitukcheewanont P, Gilsanz V. Bone acquisition in healthy children and adolescents: comparisons of dual-energy x-ray absorptiometry and computed tomography measures. *The Journal of clinical endocrinology and metabolism*. Apr 2005;90(4):1925-1928.

Figure legends

Figure 1 – Estimation of peak bone mass. Panel A – bone mineral content plotted over age, B – lumbar spine aBMD plotted over age, C – total hip aBMD plotted over age, D – femoral neck aBMD plotted over age. Quadratic line of best fit shown.

Table 1. Baseline characteristics (n=45)

	All	<20yo n=12	≥20yo n=33	P value#
Age (years)	19.4 ± 5.2	13.9 ± 3.1	22.1 ± 3.8	<0.001
Male (%)	57.8	41.7%	63.6%	0.306
Body mass index (kg/m ²)	18.3 ± 4.5	15.8 ± 3.1	19.2 ± 4.6	0.019
Anticonvulsant use	60%	78.6%	51.5%	0.084
Ambulatory	20%	21.4%	18.2%	0.796
GMFCS*				0.272
I-II	6.7%	16.6%	3%	
III	11.1%	0%	15.2%	
IV	17.8%	16.7%	18.2%	
V	64.4%	66.7%	63.6%	
Fracture	42.2%	50.0%	42.4%	0.633
Bisphosphonate exposure	24.4%	28.6%	27.3%	0.927
Hypogonadal	33.3%	50.0%	27.3%	0.133
PEG feeding	31.1%	35.7%	27.3%	0.563
Serum calcium (mmol/L)	2.38 ± 0.12	2.36 ± 0.14	2.38 ± 0.12	0.728
Serum phosphate (mmol/L)	1.26 ± 0.21	1.34 ± 0.26	1.23 ± 0.19	0.214
PTH (pmol/L)	3.89 ± 2.41	4.60 ± 3.25	3.81 ± 2.41	0.673
ALP (U/L)	110.0 ± 49.0	151.5 ± 77.6	97.6 ± 30.9	0.016
25-OH Vitamin D (nmol/L)	76.8 ± 29.1	88.7 ± 35.0	73.7 ± 27.3	0.230
Lumbar spine aBMD (g/cm ²)	0.820 ± 0.229	0.659 ± 0.203 (n=9)	0.908 ± 0.201 (n=20)	0.004
Lumbar spine Z-score	-2.0 ± 1.4	-3.1 ± 1.3	-2.2 ± 1.6	0.150
Femoral neck aBMD (g/cm ²)	0.681 ± 0.215	0.560 ± 0.210 (n=7)	0.711 ± 0.159 (n=20)	0.060
Femoral neck Z-score	-2.5 ± 1.6	-3.4 ± 1.7	-2.2 ± 1.2	0.059
Total hip aBMD (g/cm ²)	0.662 ± 0.200	0.550 ± 0.200	0.697 ± 0.142	0.046
Total hip Z-score	-2.7 ± 1.5	-3.6 ± 1.6	-2.4 ± 1.1	0.052
Total body aBMD	0.872 ± 0.183	0.769 ± 0.130	0.921 ± 0.127	<0.001

(g/cm ²)		(n=12)	(n=30)	
Total body Z-score	-2.0 ± 1.5	-2.5 ± 1.1	-1.8 ± 1.4	0.162
Total body BMC (g)	1518.8 ± 575.2	1035.8 ± 371.1	1718.6 ± 526.4	<0.001

Data are presented as mean±standard deviation or percentages

*GMFCS = gross motor function classification scale

P value for differences between <20yo and ≥20yo were calculated using independent sample t-test for continuous variables and chi square for categorical variables.

Table 2 Change in aBMD, BMC and Z-score per year of follow-up

DXA measurement	N	Change/year	95% CI	P value
Lumbar spine aBMD	29	0.012g/cm ²	0.008, 0.017	<0.001
Lumbar spine Z-score	29	0.060	0.020, 0.101	0.004
Femoral neck aBMD	27	0.001g/cm ²	-0.005, 0.006	0.830
Femoral neck Z-score	27	0.012	-0.032, 0.055	0.604
Total hip aBMD	27	0.004g/cm ²	-0.002, 0.009	0.058
Total hip Z-score	27	0.045	0.008, 0.086	0.020
Total body aBMD	42	0.010g/cm ²	0.006, 0.013	<0.001
Total body Z-score	42	0.060	0.015, 0.106	0.009
Total body BMC	42	22.4g	14.2, 30.7	<0.001

Table 3 - Change in areal BMD/BMC according to age (median % change/year)

	<20yo (n=12)	>20yo (n=33)	P value
Skeletal site	median % change/year		
LSaBMD	8.5 (1.9, 13.7)	0.9 (-1.2, 3.1)	0.001
FNaBMD	8.5 (-4.4, 17.9)	-0.5 (-5.2, 3.3)	0.026
THaBMD	3.9 (-3.3, 14.1)	0.0 (-3.2, 6.3)	0.256
TBaBMD	4.3 (1.3, 8.1)	0.1 (-2.2, 2.3)	<0.001
TBBMC	7.8 (3.2, 14.2)	0.3 (-3.1, 2.7)	<0.001

Data is expressed as percentages (25th, 75th percentiles). Comparisons using Mann Whitney U.

Table 4 – Effect of variables on bone density per year of follow-up

Predictor	Δ LSaBMD/yr	Δ FN aBMD/yr	Δ TH aBMD/yr	Δ TBaBMD/yr	Δ TBBMC/yr
Female	0.011	0.007	0.011	0.009	14.4
	P=0.047	P= 0.206	P= 0.030	P=0.014	P=0.101
Non-ambulatory	-0.022	-0.006	-0.011	-0.012	-36.6
	P<0.001	P=0.628	P=0.316	P=0.082	P=0.037
GMFCS	-0.009	-0.006	-0.011	-0.009	-18.9
	P<0.001	P=0.172	P=0.007	P<0.001	P=0.003
Hypogonadal	0.003	0.002	0.003	0.009	7.8
	P=0.512	P=0.709	P=0.586	P=0.007	P=0.396
Anticonvulsant use	-0.016	0.003	-0.003	-0.006	12.6
	P<0.001	P=0.487	P=0.598	P=0.072	P=0.131
Bisphosphonate use	0.001	0.005	0.001	-0.004	0.19
	P=0.836	P=0.394	P=0.805	P=0.354	P=0.985
Fracture	0.021	0.005	0.004	0.001	14.1
	P<0.001	P=0.380	P=0.440	P=0.988	P=0.169
Weight	-0.0001	-0.001	-0.001	-0.0001	-1.5
	P=<0.001	P=<0.001	P<0.001	P=0.014	P<0.001
Vitamin D	-0.001	0.001	0.001	-0.001	-0.6
	P<0.001	P<0.001	P<0.001	P<0.001	P=0.001

Δ LSaBMD/yr = change in lumbar spine areal BMD/year, FN = femoral neck, TH = total hip, TB = total body
GMFCS = gross motor function classification scale

Figure 1 – Estimation of peak bone mass

Figure 1 – Estimation of peak bone mass. Panel A – total body bone mineral content plotted over age, B – lumbar spine aBMD plotted over age, C – total hip aBMD plotted over age, D – femoral neck aBMD plotted over age. Quadratic line of best fit shown.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Trinh, A;Wong, P;Fahey, MC;Brown, J;Strauss, BJ;Ebeling, PR;Fuller, PJ;Milat, F

Title:

Longitudinal changes in bone density in adolescents and young adults with cerebral palsy:
A case for early intervention

Date:

2019-07-10

Citation:

Trinh, A., Wong, P., Fahey, M. C., Brown, J., Strauss, B. J., Ebeling, P. R., Fuller, P. J. & Milat, F. (2019). Longitudinal changes in bone density in adolescents and young adults with cerebral palsy: A case for early intervention. *CLINICAL ENDOCRINOLOGY*, 91 (4), pp.517-524. <https://doi.org/10.1111/cen.14052>.

Persistent Link:

<http://hdl.handle.net/11343/286139>