The Relation between Vertebral Bone Mineral Content and Growth Patterns in Non-ambulatory Cerebral Palsy Patients

Prof.Ghada Farag El Dorry, Professor, Institute of Post-graduate Childhood Studies, Ain-Shams University
Prof.Mohamed Reda Awad, Professor, Faculty of Medicine- Al Azhar University
Prof.Ahmed Mohamed El Kahky, Professor, Institute of Post-graduate Childhood Studies, Ain-Shams University
Abeer Al Sayed Ahmed Hegazy

Summary

Background: Brain development continues during the first two years of life, so that cerebral palsy can result from brain injury occurring during the prenatal, Perinatal, or postnatal periods. Cerebral palsy is characterized by motor impairment and can present with global physical and mental dysfunction. Markedly reduced bone mass in non- ambulatory children with spastic quadriplegia has been reported to place these persons at risk of osteopenia, osteoporosis, and fracture

Aim of the study: This study evaluated the relation between retarded growth patterns and reduced vertebral bone mineral content in non-ambulatory cerebral palsy patients.

Methodology: A descriptive analytical study of 30 children with cerebral palsy of both genders, between 5 and 8 years of age, attending the Special Needs Care Center of the Institute of Postgraduate Childhood Studies, Ain Shams University and also those attending the Unit for Children with Special Need at Agouza Military Rehabilitation Center, recruited over a 6 months period, and classified according to the Gross Motor Function classification system. All cases were subjected to a full history taking, a full clinical examination, dual- energy x- ray absorptiometry (DXA) scan to measure bone mineral content (BMC) using Hologic QDR series Discovery (TM) and Lunar Prodigy DXA machines and blood samples were collected for bone profile laboratory test.

Results: Lower bone mineral density (BMD) Z- scores were associated with greater severity of CP Gross Motor Functional Measure (GMFCS level), feeding difficulty, and poorer growth and nutrition as judged by weight Z- scores. A negative correlation between BMD and GMFS confirmed this observation.

Conclusion: In conclusion the first step in the management of osteoporosis in children with CP is to reduce the known manageable risk factors. When possible, medications such as anticonvulsants with high impact on BMD, carbonated beverages, low nutritional status, low sun exposure and low vitamin intake should be eliminated.

Key words: CP, DXA scan, growth pattern, non- ambulatory.

العلاقة بين المحتوى المعدنى الفقارى ومقاييس النمو فى أطفال الشلل الدماغى المقعدين

قامت الدراسة الحالية باختبار وفحص مجموعة من العوامل المتنوعة التى من شأنها التأثير على مقاييس كثافة المعدن بالعظام لدى مرضى الشلل الدماغى. وقد تساعد مقاييس كثافة المعدن بالعظام خلال العلاج فى التنبؤ وتحديد العلاج والوقاية من الكسور المرضية لدى مرضى الشلل الدماغى. ويُذكر هنا ضرورة متابعة المرضى المعرضين لعوامل الخطورة المتمثلة فى خلل الوظيفة الحركية للفم والجنف الشديد والشلل البصلى الكاذب ووضعهم تحت الملاحظة الدقيقة. ولذلك، فإن أولى خطوات علاج تخلخل العظام لدى الأطفال المصابين بالشلل الدماغى تتمثل فى الحد من عوامل الخطورة المعروفة والتى يمكن علاجها والتوقى منها. وحيثما أمكن يجب تجنب بعض الأدوية كمضادات الاختلاج (أو التشنجات) والتى لها تأثير كبير على كثافة المعدن بالعظام، فضلاً عن ضرورة الحد من تناول المشروبات الغازية، وتفادى سوء الحالة الغذائية وضعف التعرض للشمس وقلة جرعات الفيتامين.

الكلمات الدالة: الإجهاد البيئي، خديج، والاستجابات السلوكية للإجهاد، والإشارات الفسيولوجية للإجهاد.

Introduction:

Osteoporosis literally means "Porous Bone", It is a disease characterized by too little bone formation or excessive bone loss or a combination of both. People with osteoporosis have an increased risk of fractures. It is most common in older people, especially older women[1]. It is rare in children and adolescents. When it does occur, it is usually caused by an underlying medical disorder or by medications used to treat the disorder. This is called secondary osteoporosis. Sometimes, however, there is no identifiable cause of osteoporosis in a child. This is known as idiopathic osteoporosis.[2]

No matter what causes it, juvenile osteoporosis can be a significant problem because it occurs during the child's prime bone- building years. From birth through young adulthood, children steadily accumulate bone mass, which peaks sometime before age 30 years.[3] The greater their peak bone mass, the lower their risk for osteoporosis later in life. After their mid- 30s, bone mass typically begins to decline very slowly at first but increasing in their 50s and 60s. Both heredity and lifestyle choices especially the amount of calcium in the diet and the level of physical activity influence the development of peak bone mass and the rate at which bone is lost later in life.[1]

One approach to reducing the prevalence of osteoporosis could be to increase the peak bone mass laid down during childhood and adolescence, as it has been estimated that a 10% increase in peak bone mass will reduce the osteoporotic fracture risk in elderly people by 50%[2]. Although as much as 60-80% of the variance in bone mineral density (BMD) may be explained by genetic factors, modifiable environmental factors such as diet and physical activity (PA) are also important determinants of BMD. One of the key determinants of skeletal development during growth is mechanical load.[2]

Cerebral palsy is a static neurologic condition resulting from brain injury that occurs before cerebral development is complete. Because brain development continues during the first two years of life, cerebral palsy can result from brain injury occurring during the prenatal, Perinatal, or postnatal periods.[4]

In addition, an estimated 8,000 babies and infants, plus 1,200 to 1,500 preschool- age children are diagnosed with cerebral palsy every year in the United States. The differential diagnosis of cerebral palsy includes metabolic and genetic disorders.[4]

Cerebral palsy is characterized by motor impairment and can present with global physical and mental dysfunction. In 2001, the United Cerebral Palsy Foundation estimated that 764,000 children and adults in the United States carried the diagnosis of cerebral palsy.[4] Seventy to 80 percent of cerebral palsy cases are acquired prenatally and from largely unknown cause. Birth complications including asphyxia, are currently estimated to account for about 6 percent of patients with congenital cerebral palsy.[3] Neonatal risk factors for cerebral palsy include birth after fewer than 32 weeks' gestation, birth weight of less than 5 lb, 8 oz (2,500 g), intrauterine growth retardation, intracranial hemorrhage, and trauma.[5]

Markedly reduced bone mass in non ambulatory children with spastic quadriplegia has been reported to place these persons at risk of osteopenia, osteoporosis, and fracture.[19] Dual x- ray absorptiometry (DXA) offers a simple method for investigating bone mass. It has been shown to have high accuracy, is easily available, has short scanning time, gives low radiation, is not invasive and does not require active participation and is therefore easy to use. It is also excellent for longitudinal studies to follow up children during development.[3]

Measurements of areal bone mineral density (aBMD) are influenced by bone size, with larger bones having artificially inflated areal bone mineral density (aBMD) measurements. This is an important problem in pediatric bone assessment because of the large differences in body size and bone size within and across different ages.[6] Studies show that aBMD by DXA increases with age, but studies using computed tomography indicate that true volumetric BMD (vBMD) is relatively constant during childhood until puberty, at which time there is a large increase in vBMD. BMC increases with age, and the increase in aBMD that is observed is likely the result of greater bone size[6].

Volumetric BMD (vBMD) at both peripheral and axial bone sites can be measured with Quantitative computed tomography QCT scanners. However, the primary disadvantage is the high radiation doses, making it unsuitable for use in determining factors that influence bone in healthy children. Without normative pediatric databases for QCT, it is difficult to use this method clinically[6]. Wren, et al., studied the bone acquisition in healthy children and adolescents and compared dual- energy x- ray absorptiometry and computed tomography measures[7].

Methodology:

- Type Of Study: Descriptive Study.
- Study Sample: The study included thirty patients with CP of both genders, between (5- 8) years of age, attending the Special Needs Care Center of the Institute of Postgraduate Childhood Studies, Ain Shams University and the Unit for Children with Special Need at Agouza Military Rehabilitation Center.

  All participants were subjected to:

  1. Full medical history with particular emphasis on peri- natal history nutritional history, type of rehabilitation program and physiotherapy. In addition history of any previous bone fractures and it's cause, also drug history.
  2. Full general medical and neurological examination were conducted for the selected group during the first visit, evaluation of any signs of complications, evaluation of anthropometric measures using the growth references for children with cerebral palsy for height, weight and body mass index.[24]
  3. Patients were graded according to the Gross Motor Functional Classification for their level of affection.[23]
  4. Patients were appointed for baseline DXA scan (BMC) using Hologic QDR series Discovery (TM) and Lunar Prodigy DXA machines.

Statistical Analysis:

Data were collected, revised, verified then edited on P. C, All the statistical analyses were performed Statistical Package version 12, for the Social Sciences (SPSS). The results of quantitative data are expressed as the mean and standard deviation (Mean± SD). The results of qualitative data are expressed as number and percentage. Unpaired t- test was used to compare a quantitative variable between two independent groups in parametric data. Paired t- test was used to compare a quantitative variable between two dependent groups in parametric data. Pearson correlation coefficient (r) was used to correlate between many variable groups. Levels of statistical significance were set as: P> 0.05 considered as non significant. P< 0.05: considered as significant. P< 0.01 considered as highly significant.[25]

Results:

In this study, collected data were age; weight, height, body mass index (BMI), Bone Mineral Content (BMC), Bone Mineral Density (BMD), triceps, serum Alkaline Phosphatase (ALP) and CA. Averages standard deviations minimums and maximums are presented in table 1. High standard deviations were observed in the ALP and weight data.

Table (1) Demographic Data of the study group

	Male Mean± SD	Min.	Max.	Female Mean± SD	Min.	Max.
Age	6.57±1.10	5	8	5.99±1.28	5	8
Weight	14.63±2.92	11	25	17.63±7.56	9	31.10
Height	98.93±7.90	90	123	102.43±9.2	90	116
BMI	15.15±1.25	11	18	16.53±5.30	11	28
BMC	10.88±2.66	5.48	15.83	11.55±3.54	8.40	19.76
BMD	2.54±0.89	4.6	6	2.06±0.94	3.2	6
MAC	15.52±1.32	13	19.2	16.41±2.95	14.0	23
HC	50.05±0.67	49	52	49.88±0.56	49	51
Triceps	5.72±1.42	4	10	7.05±2.28	5	12
ALP	342.91±164.57	102	806	308.13±155.53	106	618
CA	8.55±0.75	7.7	10.5	9.38±0.60	8.6	10.2

Most of the patients didn't have history of maternal disease or maternal drug usage during pregnancy or exposure to radiation or antenatal infection or birth trauma. Only two patients were twins. Majority of the patients had relatively young (below 20) or relatively old (between 35 and 40) mothers (Table 2)

Table (2) Maternal factors causing CP

Mother Age	Sex		Total
	Female	Male	
Less Than 20 Years	3 (37.5%)	2 (31.8%)	10 (33.3%)
From 20 To 25 Years	1 (12.5%)	4 (4.518.2%)	5 (16.7%)
From 25 To 30 Years		1 (4.5%)	1 (3.3%)
From 30 To 35 Years	1 (12.5%)	4 (18.2%)	5 (16.7%)
From 35 To 40 Years	3 (37.5%)	5 (22.7%)	8 (26.7%)
Older Than 40 Years		1 (4.5%)	1 (3.3%)
Total	8 (100%)	22 (100%)	30 (100%)
Maternal Disease	Sex		Total
	Female	Male	
- Ve	5 (62.5%)	14 (63.6%)	19 (63.3%)
+Ve	3 (37.5%)	8 (36.4%)	11 (36.7%)
Total	8 (100%)	22 (100%)	30 (100%)
Maternal Drugs	Sex		Total
	Female	Male	
- Ve	5 (62.5%)	13 (61.9%)	18 (62.1%)
+Ve	3 (37.5%)	8 (38.1%)	11 (37.9%)
Total	8 (100%)	21 (100%)	29 (100%)
Maternal Exposure To Radiation	Sex		Total
	Female	Male	
- Ve	7 (87.5%)	22 (61.9%)	18 (96.7%)
+Ve	1 (12.5%)	0 (0.0%)	1 (3.3%)
Total	8100%)	22 (100%)	30 (100%)
Twins	Sex		Total
	Female	Male	
- Ve	7 (87.5%)	21 (95.5%)	28 (93.3%)
+Ve	1 (12.5%)	1 (4.5%)	2 (6.6%)
Total	8 (100%)	22 (100%)	30 (100%)

History of cyanosis and postnatal Kernicterus was common among study patients. (Table 3)

Table (3) Risk factors of CP

Ante Natal Infection	Sex		Total
	Female	Male	
- Ve	7 (87.5%)	18 (81.8%)	25 (83.3%)
+Ve	1 (12.5%)	4 (18.2%)	5 (16.7%)
Total	8 (100%)	22 (100%)	30 (100%)
Cyanosis	Sex		Total
	Female	Male	
- Ve	6 (75.0%)	4 (10.2%)	10 (33.3%)
+Ve	2 (25.0%)	18 (81.8%)	20 (66.7%)
Total	8 (100%)	22 (100%)	30 (100%)
Birth Trauma	Sex		Total
	Female	Male	
- Ve	7 (87.5%)	21 (95.5%)	28 (93.3%)
+Ve	1 (12.5%)	1 (4.5%)	2 (6.6%)
Total	8 (100%)	22 (100%)	30 (100%)
Post Natal Kernicterus	Sex		Total
	Female	Male	
- Ve	3 (37.5%)	11 (50.0%)	14 (46.7%)
+Ve	5 (62.5%)	11 (50.0%)	16 (53.3%)
Total	8 (100%)	22 (100%)	30 (100%)
Post Natal Meningitis	Sex		Total
	Female	Male	
- Ve	7 (87.5%)	22 (100%)	29 (96.7%)
+Ve	1 (12.5%)	0 (0.0%)	1 (3.3%)
Total	8 (100%)	22 (100%)	30 (100%)
Other Disease	Sex		Total
	Female	Male	
Non	3 (37.5%)	10 (45.5%)	13 (43.3%)
Deafness	1 (12.5%)	1 (4.5%)	2 (6.7%)
Deafness& Optic	1 (12.5%)	1 (4.5%)	2 (6.7%)
Optic Atrophy	2 (25.0%)	6 (27.3%)	8 (26.7%)
Cataract	1 (12.5%)	1 (4.5%)	2 (6.7%)
V. S. D	0 (0.0%)	3 (13.6%)	3 (10.0%)
Total	8 (100%)	22 (100%)	30 (100%)

BMC data were collected and correlated with various variables. BMC was found to have positive correlation to sun exposures, hydrotherapy vitamin intake, physical therapy, stretching exercises, number of sessions, milk intake, fish intake, fruit consumption and vegetable intake (Table 4). On the other hand BMC was found to have negative correlation with the use of excessive cola intake and antiepileptic drugs (Table 4). A strong correlation (0.7) was observed between BMD and BMC scores among the study patients (Table 4).

Table (4) Correlation between BMC and Various Variables(****)

Variable	Correlation Strength	Variable	Correlation Strength
Weight In Kg	0.5**	Spasticity Level	- 0.4**
Height In Cm	0.6**	GMFS	- 0.6**
Mid Arm Circumference (MAC) in cm	0.5**	Pseudobulbar Palsy	- 0.4*
Triceps SFT Mm	0.6**	Milk And Dairy/Wk	0.5**
Serum Calcium (mg/dl)	0.4*	Egg/Wk	0.3*
BMD	0.7***	Fish/Wk	0.3*
Weight Bearing Exercises	0.5*	Fruits/Wk	0.4*
Hydrotherapy	0.5**	Vege/Wk	0.5**
Antiepileptic Drugs	- 0.6**	Vitamins	0.6***
Number Of Sessions/Wk	0.6**	Sun Exposure/Wk	0.6***
Oral Motor Dysfunction	- 0.4*		

*Indicates weak correlation. **Indicates medium correlation. *** indicates strong correlation. **** Pearson and Spearman correlations were used according to the type of data (numerical or ordinal).

Our BMD data suggested that the combination of hydrotherapy with other

therapeutic approaches can lead to marked improvement in the BMC scores (Figure 1).

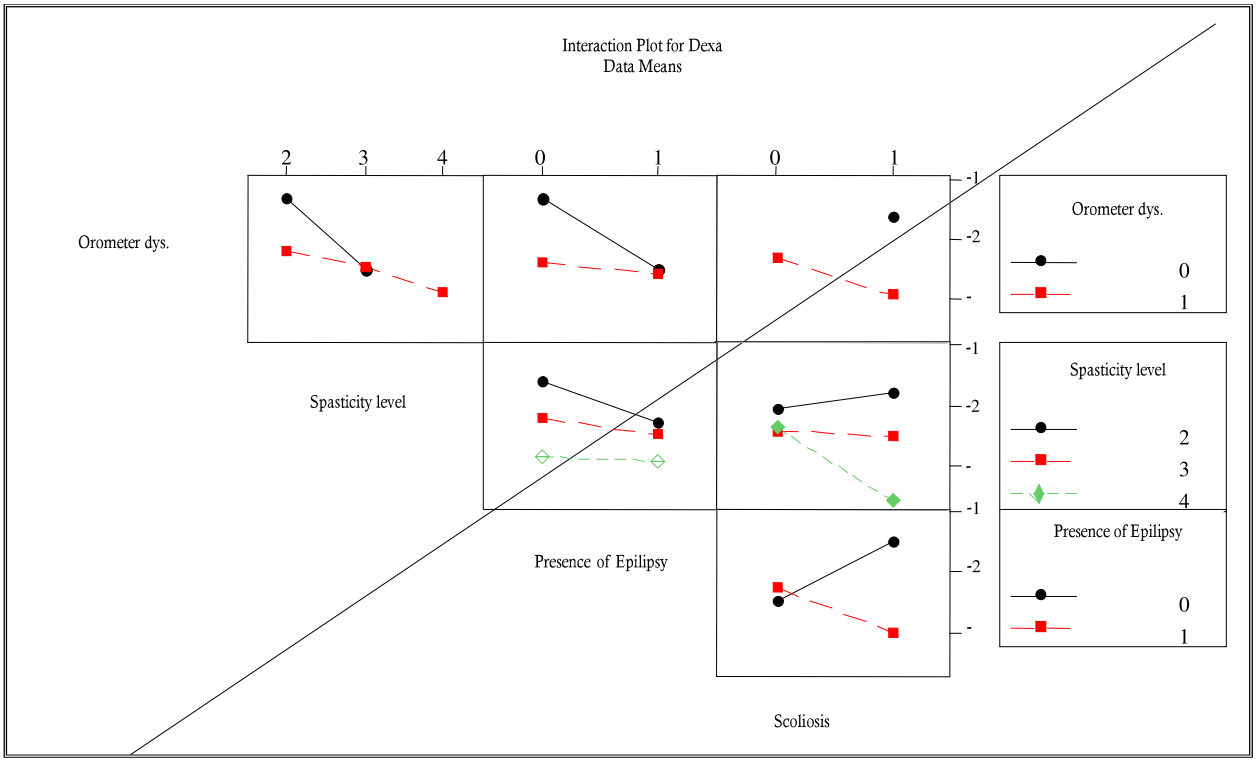

Figure (1) Interaction among Oral motor Dysfunction, Spasticity Level, Epilepsy, Scoliosis and BMC.

Discussion:

Cerebral palsy is the most common physical disability of childhood[8]. Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitations, which are attributed to non- progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication and behavior, epilepsy, and secondary musculoskeletal problems[7].

The average cumulative incidence rate of CP is 2.7 per 1000 live births. In recent years, the incidence rate of CP has been increasing internationally due to increased survival of low birth weight infants.[10,11] Bone acquisition and remodeling is controlled by mechanical and metabolic factors. Malnutrition, immobility, sex steroid deficiency, and other factors can interrupt bone mineral accrual and have been found to be a contributing factor to early bone loss in children with CP.[12]

Adolescence is typically a period of maximal bone accrual. Many studies suggest that attainment of peak bone mass occurs at a younger age than was previously believed, with the average age closer to 18 to 25 years than 30 years.[13] Twenty- five percent of peak bone mass is acquired during the 2- year period surrounding peak height velocity and at least 90% is reached by age 18 years.[14]

Wren and colleagues[7] evaluated the influence of low- level mechanical stimulation on BMD in ambulatory children with disabilities in a double- blinded randomized control trial.

Available software for reference Z- scores for DXA scans for the lumbar spine begin at the age of 6 years. Reference Z- scores for the distal lateral femur are also available for children at the age of 6 years. If a child is considered at risk, DXA scans should be performed for a baseline at the age of 6 years with follow- up every 1 to 2 years depending on individual risk factors. If a child with CP meets the criteria for osteoporosis, the clinician also needs to consider the use of a Bisphosphonate to improve BMD and possibly prevent future fractures[7].

Bone growth, as assessed by BMD, is an important aspect of growth in children with CP. In addition to diminished linear growth, children with CP often sustain painful pathologic fractures due to poor mineralization of bone, often with minimal trauma.[15] Thus, bone growth and bone density are highly relevant to overall linear growth, nutritional health, and health- related quality of life. Henderson and colleagues[16] initially investigated nutritional status and BMD in 139 children with CP in a cross- sectional study. They found that BMD was variable, but averaged –1SD. Functional severity (increasing severity) and lower nutritional status correlated with lower BMD. Low calcium intake and immobilization were also contributors to low BMD. Vitamin D levels and anticonvulsants did not correlate with BMD when the severity of CP and nutritional status were controlled. Serum calcium, alkaline phosphatase, and osteocalcin were also found not to correlate with BMD. Our data were in agreement with the previously mentioned observation. Low nutritional status, low vitamin intake and low rate of sun exposure correlated with low BMD.

Henderson and colleagues[16] evaluated whether BMD can predict fractures in an observational cohort study of 43 children with quadriplegic CP followed for a mean of 3.8 years. During the follow- up, 9 fractures occurred. Fractures in this population often occurred in the extremities or in the spine. Spine BMD did not correlate well with BMD in the extremities, specifically the femur. In our study, spine BMD was used to evaluate osteoporosis, but similar observation could be anticipated with extremities- based BMD.

Further investigation into bone density in children with CP focused on those with moderate to severe motor impairment. (Gross Motor Function Classification System, GMFCS, III toV). Significantly decreased bone density

is virtually universal in non- ambulatory children with moderate to severe CP after the age of 10 years; however, predicting which children will fracture is a challenge.[13]

Henderson and colleagues[16] have studied longitudinal assessments over 2 years of bone density in children and adolescents with moderate to severe CP (GMFCS III to V), finding that lower BMD Z- scores at initial evaluation were associated with greater severity of CP (GMFCS level), feeding difficulty, and poorer growth and nutrition as judged by weight Z- scores. Similar findings were observed in our data. A negative correlation between BMD and GMFS confirmed this observation.

Our data evaluated the food intake details in the study patients. A positive correlation with vegetables, fruit, fish, milk and egg were positively correlated with higher BMD scores. Optimizing nutritional status, especially vitamin D and calcium levels, are important in the prevention and treatment of osteoporosis. Melanin reduces the production of vitamin D3. Individuals with darker skin color require longer exposure (up to five- to tenfold) to sunlight to make the necessary vitamin D3. Latitude, time of day, and season of the year affect the production of vitamin D3 in the skin. Casual exposure to the sun provides most of the vitamin D needed. Excess is stored in fat to be used during winter months when exposure may be limited. However, topical use of sunscreen dramatically reduces the amount of vitamin D absorbed. A sun protection factor of 8 (SPF 8) reduces absorption by greater than 97%. Chronic sunscreen use can result in vitamin D deficiency[17].

Vitamin D deficiency is a concern for children with CP who may not be exposed to ample amounts of sunshine and who may have insufficient dietary intake. Jekovec- Vrhovsĕk and colleagues evaluated BMD before and after supplementation with vitamin D and calcium. They followed 20 children with CP living in residential care. These children had severe motor impairment and used multiple and chronic anticonvulsant therapy. Thirteen children received vitamin D and 500 mg of calcium supplementation for 9 months. All children had increases in BMD. Of the 7 not treated and monitored, BMD remained the same or decreased[18]. In our study, the combination of low vitamin intake and low sun exposure was correlated with lower BMD. On the contrary, high vitamin intake protected high risk patients (Patients with oro motor dysfunction) from BMD deterioration.

Vitamin D status can be determined by assessing levels of 25 (OH) D. A level of less than 12.5 ng/mL is severe deficiency. Deficiency is defined as a level less than 37.5 ng/mL, and insufficiency as a level between 37.5 and 50 ng/mL. Sufficient levels of vitamin D are between 50 and 250 ng/mL. Aggressive therapy is needed for significant depletion. Pharmacologic doses of vitamin D should be used orally at 50,000 IU of vitamin D once weekly for 8 weeks[17]. In our study, a positive correlation between milk intake and BMB was observed.

Karen et al.[19] demonstrated that the high consumption of carbonated beverages and the declining consumption of milk are of great public health significance for girls and women because of their proneness to osteoporosis in later life. The data showed a strong association between cola beverage consumption and bone fractures in girls [the adjusted odds ratio (OR)= 3.59; 95% confidence interval (CI) 1.21, 10.75; p= 0.022]. High intake of dietary calcium was protective (adjusted OR= 0.284; 95% CI0.087,0.920; p= 0.036). No association between the non- cola drinks and bone fractures was found. In boys, only total caloric intake was associated with the risk of bone fractures; the association was inverse[20]. In our study, cola intake was negatively correlated with BMD.

We also evaluated the effect of various therapeutic approaches and their interactions on the BMD scores in our study patients. Our data suggested that the weight bearing exercises are positively correlated with higher BMD. These finding are in agreement with the study conducted by Caulton and colleagues. Caulton and colleagues[21] evaluated the impact of standing/weight bearing on BMD in a randomized clinical trial of 26 prepubertal children with severe CP, comparing children receiving 50% increase in regular standing versus no increase in standing for a 9- month period. Range of standing was between 180 and 675 minutes per week. Improvement in lumbar spine BMD of 6% was reported in the standing group over the control group. No change was seen in tibial BMD. These investigators concluded that, whereas increased standing may decrease the risk of vertebral fractures, it is unlikely to impact lower extremity fractures. The magnitude of an increase in BMD sufficient to decrease the risk of fracture has not been defined for children with CP.

In our study, we also observed a positive correlation between hydrotherapy and BMD improvement. Similar studies in postmenopausal osteoporotic women suggested similar trend. Rotstein et al.[22] examined the effect of a seven months program of water exercise, on bone mineral density (BMD) in postmenopausal women. Thirty- five postmenopausal women trained for seven months for three one- hour sessions per week. DEXA test findings for vertebrae L2- L4 showed that although the time factor had a significant effect only on the bone mineral content (BMC), (4.61 $P< 0.05$), the interaction of time group was found to be significant for each of the variables: BMD (9.25 $P< 0.01$), BMC (7.99 $P< 0.01$), z- score (5.35 $P< 0.05$) and t- score (9.41 $P< 0.01$). These interactions indicated a general trend towards maintenance or improvement of bone status in the experimental group and a trend towards declining bone status for the control group.

References:

1. Yu S, Huang YC. Knowledge of, attitudes toward, and activity to prevent osteoporosis among middle- aged and elderly women. **J Nurs Res.** 2003 Mar; 11 (1) : 65-72.
2. Hasselstrøm HA, Karlsson MK, Hansen SE, Grønfeldt V, Froberg K, Andersen LB A 3- year physical activity intervention program increases the gain in bone mineral and bone width in prepubertal girls but not boys: the prospective copenhagen school child interventions study (CoSCIS). **Calcif Tissue Int**. 2008 Oct; 83 (4) : 243-50.
3. O'Donnell S; Canadian Chronic Disease Surveillance System (CCDSS) Osteoporosis Working Group Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: results from a feasibility study. **Arch Osteoporos**. 2013 Dec; 8 (1-2) : 143.
4. Huang RY, Miller LM, Carlson CS, Chance MR. In situ chemistry of osteoporosis revealed by synchrotron infrared microspectroscopy. **Bone**. 2003 Oct; 33 (4) : 514-21.
5. Krick J, Murphy- Miller P, Zeger S, Wright E. Pattern of growth in children with cerebral palsy**. J Am Diet Assoc** 1996; 96:680-685.
6. Binkley TL, Berry R, Specker BL. Methods for measurement of pediatric bone. **Rev Endocr Metab Disord**. 2008 Jun; 9 (2) : 95-106
7. Wren TA, Liu X, Pitukcheewanont P, Gilsanz V. Bone densitometry in pediatric populations: discrepancies in the diagnosis of osteoporosis by DXA and CT.. **J Pediatr**. 2005 Jun; 146 (6) : 776-9.

8. Andrew MJ, Sullivan PB. Growth in cerebral palsy. **Nutr Clin Pract**. 2010 Aug; 25 (4) : 357-61.
9. Rosenbaum M, Pietrobelli A, Vasselli JR, Heymsheld SB, Leibel RL. Sexual dimorphism in circulating leptin concentrations is not accounted for by differences in adipose tissue distribution**. Int Job Relat Metab Disord** 2001; 25: 1365-1367
10. Suzuki J, Ito M. Incidence patterns of cerebral palsy in Shiga Prefecture, Japan, 1977-1991**. Brain Dev**. 2002 Jan; 24 (1) : 39-48.
11. Goldstein M. Treatment of cerebral palsy: what we know do not know. **J Pediatr** 2004; 145: 542-546.
12. Lloyd ME, Spector TD, Howard R. Osteoporosis in neurological disorders**. J Neurol Neurosurg Psychiatry**. 2000 May; 68 (5) : 543-7.
13. Henderson RC, Lark RK, Gurka MJ, Worley G, Fung EB, Conaway M, Stallings VA, Stevenson RD. Bone density and metabolism in children and adolescents with moderate to severe cerebral palsy. **Pediatrics**. 2002 Jul; 110 (1 Pt 1) : e5.
14. Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R. Calcium accretion in girls and boys during puberty: a longitudinal analysis. **J Bone Miner Res.** 2000 Nov; 15 (11) : 2245-50
15. Ali O, Shim M, Fowler E, Greenberg M, Perkins D, Oppenheim W, Cohen P. Growth hormone therapy improves bone mineral density in children with cerebral palsy: a preliminary pilot study**. J Clin Endocrinol Metab**. 2007 Mar; 92 (3) : 932-7. Epub 2006 Dec 19.
16. Henderson NK, Prince RL Preventing osteoporosis naturally. **Med J Aust.** 2001 Sep 3;175 (5) : 239-4
17. Houlihan CA, * and Stevenson, RD Bone Density in Cerebral Palsy Phys **Med Rehabil Clin N Am**. 2009 August; 20 (3) : 493-508.
18. Kavcic A and Vodusec DB. A historical perspective on cerebral palsy as a concept and a diagnosis**. Eur J Neurol** 2005; 12: 582-587.
19. Karen C Schliep, Enrique F Schisterman, Sunni L Mumford, Anna Z Pollack, Cuilin Zhang, Aijun Ye, Joseph B Stanford, Ahmad O Hammoud, Christina A Porucznik, and Jean Wactawski- Wende Caffeinated beverage intake and reproductive hormones among premenopausal women in the BioCycle Study. **Am J Clin Nutr** February 2012 vol. 95 no. 2 488-497
20. Wyshak G, Frisch RE. Carbonated beverages, dietary calcium, the dietary calcium/phosphorus ratio, and bone fractures in girls and boys. **J Adolesc Health**. 1994 May; 15 (3) : 210-5.
21. Caulton JM, Ward KA, Alsop CW, Dunn G, Adams JE, Mughal MZ. A randomised controlled trial of standing programme on bone mineral density in non- ambulant children with cerebral palsy. **Arch Dis Child.** 2004 Feb; 89 (2) : 131-5
22. Rotstein A, Harush M, Vaisman N. The effect of a water exercise program on bone density of postmenopausal women. **J Sports Med Phys Fitness**. 2008 Sep; 48 (3) : 352-9.
23. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Barbara Galuppi **Dev Med Child Neurol** 1997;39:214-223
24. Developmental Medicine and Child Neurology 2006; www. Life Expectancy.o rg/articles/GrowthCharts. shtml
25. Nikolić D, Muresan RC, Feng W, Singer W (2012) Scaled correlation analysis: a better way to compute a cross- correlogram. European **Journal of Neuroscience**, pp. 1•21.