

Quantitative ultrasound bone profile and vitamin D status in 5-11 years old children with intellectual disability

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Abstract

Objective: To measure serum vitamin D levels and quantitative ultrasound bone profile parameters and their correlation with each other in children with various grades of intellectual disability and bone health.

Methods: The descriptive study was conducted from January to December, 2011, at the University of Health Sciences, Lahore, Pakistan, and comprised children aged 5-11 years having intelligence quotient less than 70. Quantitative ultrasound measurements at hand phalanges were taken using an ultrasonic bone profiler. Serum calcium, phosphate and alkaline phosphatase were measured by calorimetry and 25-hydroxy vitamin D levels were measured by enzyme-linked immunosorbent assay. Data was analysed using appropriate statistical tools.

Results: Of the 61 children, 35 (57.4%) were boys and 26(42.6%) were girls. Overall median age was 104.48 months (inter quartile range: 77.77-128.04 months). Of the total, 17(27.9%) subjects had below normal bone profile and 51(85%) had less than 20ng/ml 25-hydroxy vitamin D levels. A mild negative correlation of 25-hydroxy vitamin D was seen with age ($p=0.006$). Moderate significant correlations of amplitude dependant speed of sound were observed with age ($p<0.001$) and alkaline phosphatase ($p<0.001$).

Conclusions: Significant proportion of children with intellectual disability had below-normal bone profile. Vitamin D levels were extremely low in overwhelming majority of children with intellectual disability. Significant negative correlation of age with Vitamin D and positive correlation with amplitude dependant speed of sound may suggest increasing requirements of vitamin D with age to cope with advancing needs of growing skeleton in children with intellectual disability.

Keywords: Ad-SOS, BMD, IQ, Learning disability. (JPMA 66: 694; 2016)

Introduction

Bone is a metabolically active tissue which undergoes continuous remodelling and shows accelerated increase near the time of puberty. Bones achieve peak bone mass which decreases throughout life because of shifting of finely-tuned equilibrium between osteoblasts and osteoclasts towards resorption. Promoting peak bone mass in childhood and adolescence is considered a promising approach to prevent bone-related problems in later life.¹

Quantitative ultrasound (QUS) for assessment of bones has numerous advantages over conventional dual energy X-ray absorptiometry (DXA) technique. QUS is less influenced by size of bones² and reveals physical properties of bone determined by bone composition and structure.³ It is free of ionizing radiation, easy to use, portable and cost-effective. Phalangeal QUS measurements have also shown the ability to reveal structural changes in bones due to skeletal growth, aging and various diseases.⁴⁻⁶ As a result of these advantages, QUS becomes much more appropriate technique to

measure bone health when dealing with intellectually disabled children.

Children with intellectual disability (ID) have multitude of factors that negatively affect the normal development and physiology of bones such as inadequate nutrition, reduced mobility, increased rate of falls, associated blindness, balance and coordination problems, epilepsy, prolonged use of medications, genetic factors, various associated chronic diseases and limited exposure to sunlight.⁷ In addition to pandemic of vitamin D deficiency or insufficiency in diverse groups of population,⁸⁻¹¹ several studies from around the world have also reported inadequate or decreased vitamin D levels in children with ID.¹²⁻¹⁴

Maintenance of good bone health is considered an important factor in promoting the overall quality of life of children, adolescents and adults with physical and intellectual disabilities.¹⁵ Several studies encompassing the musculoskeletal health of children and adolescent with ID are available, but most of the work available is on adult population or on children with severe motor limitations. Literature is scarce globally and acutely lacking in Pakistan and South Asia on bone health problems faced by a population of children with ID having very little or no motor deficits. Present study was planned

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to assess bone health and vitamin D status of 5-11-year-old children with ID in local population.

The current study was planned to look into the importance of early assessment of bone health and vitamin D in overall management of children with ID. Using easy-to-administer techniques for early diagnosis of musculoskeletal problems faced by underprivileged population of children to achieve targeted treatment goals and better overall health management may eventually relax the overall physical, psychological and economical limitations of caregivers and family members.

Subjects and Methods

The descriptive study was conducted from January to December, 2011, at the Department of Physiology and Cell Biology, University of Health Sciences (UHS), Lahore, Pakistan, after approval from the institutional review board. It comprised 61 children of 5-11 years of age having intelligence quotient (IQ) less than 70. Children with ID were recruited from Amin Maktab Centre for Special Education and Training, Lahore. Written informed consent was taken from parents/guardians of the children. Detailed history was taken from the parents/guardians and complete general physical and systemic examinations were conducted on each child.

Children with autistic spectrum disorders and diseases that affect bones i.e. chronic liver disease, chronic renal disease, epilepsy, primary hyperparathyroidism, hyperthyroidism, hypogonadism and diabetes mellitus, were excluded. Children regularly using drugs that affect bones i.e. steroids, anti-epileptic drugs, supplemental vitamin D and calcium were also excluded. Children with cerebral palsy (CP) were assessed using gross motor function classification system-expanded and revised¹⁶ and only those children were included in the study that fell within level I and/or level II. Children with ID having gross difficulties with chewing and swallowing were also excluded.

Every child in the study was also assessed by a trained psychologist. Slosson intelligence test (SIT) was used to assess the IQ of each child.¹⁷ Portage Early Education Programme (PEEP) was used to assess the functioning age of each child for language, socialisation, self-help, cognitive and motor skills.¹⁸ Quantitative ultrasound (QUS) bone profile measurements i.e. Z-score, amplitude-dependant speed of sound (Ad-SOS) and bone transmission time (BTT) were taken from distal ends of proximal phalanges of four fingers of the dominant hand using DBM Sonic Bone profiler (IGEA, Capri, Italy, Model: BP01). Serum 25-hydroxy vitamin D (25OH[D]) level was estimated by solid phase enzyme-linked immunosorbent assay (ELISA) using automated EIA analyser (Bio-Rad Laboratories, Hercules, CA, USA) with commercially available 25OH(D) total ELISA kit (DIA source Immuno Assays S.A., Louvain-la-Neuve, Belgium). Serum calcium, phosphate and alkaline phosphatase (ALP) levels were also measured by calorimetric method using spectrophotometer (Microlab 300) with commercially available kits (Randox laboratories Ltd., Crumlin, UK).

Data was analysed using SPSS 20. For the purpose of analysis, children were further sub-grouped according to ID grades i.e. Mild ID (IQ 50 to 70), Moderate ID (IQ 35 to 50) and Severe ID (IQ 20 to 35). If the Z-Score generated by QUS was less than -2, children were classified as having below-normal bone profile. In case of normally distributed quantitative variables, mean $\pm$ standard deviation (SD), independent sample t-test, one-way analysis of variance (ANOVA) and Pearson correlation (r) were used for analysis. Non-parametric statistics i.e. Median (interquartile range [IQR]), Mann-Whitney U test, Kruskal Wallis test and Spearman's rho correlation (rho) were used for non-normally distributed quantitative variables. $P \leq 0.05$ was considered statistically significant for all purposes.

Results

Of the 61 children, 35 (57.4%) were boys and 26(42.6%)

Table-1: Comparison of parameters between children in groups on the basis of bone profile.

Sr. No.	Parameter	n	Below normal bone profile		n	Normal bone profile		p-value
			Mean $\pm$ SD	Median (IQR)		Mean $\pm$ SD	Median (IQR)	
1	Bone profile Z-Score	17	-2.26 $\pm$ 1.00	-2.20 (-2.90--2.00)	44	-0.20 $\pm$ 0.86	-0.20 (-0.90-0.30)	<0.001* +
2	Ad-SOS (m/sec)	17	1759.12 $\pm$ 46.52	1754.00 (1724.50-1778.00)	44	1828.64 $\pm$ 40.84	1830.50 (1794.25-1856.25)	<0.001* #
3	BTT (μ sec)	17	0.50 $\pm$ 0.14	0.48 (0.39-0.64)	44	0.66 $\pm$ 0.18	0.70 (0.52-0.76)	0.002* #
4	25OH(D) (ng/ml)	17	11.04 $\pm$ 6.69	8.40 (5.29-16.76)	43	12.49 $\pm$ 9.89	8.69 (5.37-17.94)	0.831 +
5	ALP (IU/L)	17	460.47 $\pm$ 35.53	460.00 (447.00-484.00)	43	204.84 $\pm$ 111.96	186.00 (123.00-261.00)	<0.001* #
6	Calcium (mg/100ml)	17	9.93 $\pm$ 0.78	9.96 (9.13-10.55)	44	10.29 $\pm$ 0.58	10.28 (9.98-10.74)	0.094 #
7	Phosphate (mg/100ml)	16	4.91 $\pm$ 0.63	4.90 (4.40-5.43)	43	4.86 $\pm$ 0.74	4.70 (4.20-5.30)	0.819 #

+p-value is generated by Mann-Whitney U Test. #p-value is generated by Independent Sample t-Test. *p-value ≤ 0.05 is considered statistically significant.

Ad-SOS: Amplitude dependant speed of sound. BTT: Bone transmission time. ALP: Alkaline phosphatase. 25OH(D): 25-hydroxy vitamin D.

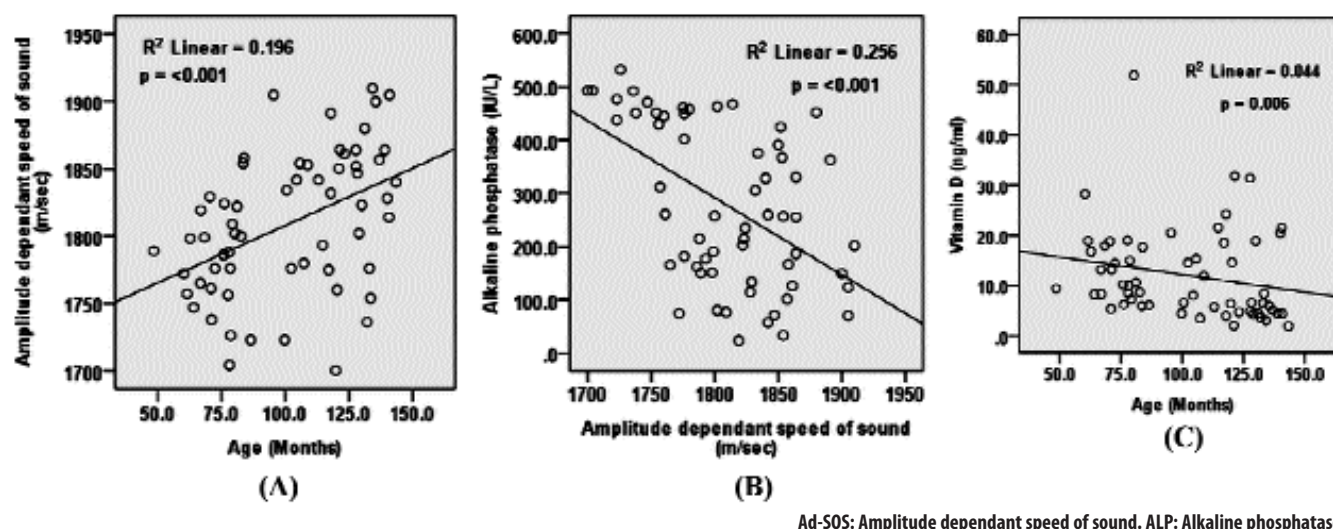


Figure-1: Scatter plots showing significant correlations of Ad-SOS with Age (A), Ad-SOS with ALP (B) and Vitamin D with Age (C).

Table-2: Comparison of parameters between children in mild, moderate and severe groups of intellectual disability (ID).

Sr. No.	Parameter	Mild ID			Moderate ID			Severe ID			p-value
		n	Mean $\pm$ SD	Median (IQR)	n	Mean $\pm$ SD	Median (IQR)	n	Mean $\pm$ SD	Median (IQR)	
1	Bone profile Z-Score	18	-1.08 $\pm$ 1.39	-0.70 (-2.28-0.03)	38	-0.71 $\pm$ 1.29	-0.70 (-2.00-0.23)	5	-0.22 $\pm$ 0.79	-0.40 (-0.75-0.40)	0.369 +
2	Ad-SOS (m/sec)	18	1790.44 $\pm$ 55.56	1788.50 (1744.25-1831.00)	38	1815.26 $\pm$ 50.91	1820.50 (1776.00-1854.25)	5	1831.40 $\pm$ 42.00	1847.00 (1799.50-1855.50)	0.170 #
3	BTT (μ sec)	18	0.56 $\pm$ 0.16	0.58 (0.43-0.70)	38	0.64 $\pm$ 0.19	0.64 (0.48-0.75)	5	0.67 $\pm$ 0.17	0.70 (0.54-0.79)	0.253 +
4	25OH(D) (ng/ml)	17	11.31 $\pm$ 11.55	8.27 (5.13-14.09)	38	12.90 $\pm$ 8.18	11.26 (5.63-18.83)	5	8.46 $\pm$ 5.86	5.95 (5.42-12.75)	0.387 #
5	ALP (IU/L)	17	298.76 $\pm$ 167.06	258.00 (158.00-473.50)	38	277.76 $\pm$ 148.26	280.00 (150.50-439.00)	5	200.40 $\pm$ 106.81	257.00 (86.50-286.00)	0.383 #
6	Calcium (mg/100ml)	18	10.34 $\pm$ 0.60	10.33 (9.97-10.77)	38	10.14 $\pm$ 0.72	10.24 (9.42-10.66)	5	10.07 $\pm$ 0.09	10.08 (9.98-10.15)	0.533 +
7	Phosphate (mg/100ml)	17	4.80 $\pm$ 0.57	4.90 (4.20-5.25)	37	4.89 $\pm$ 0.80	4.80 (4.20-5.50)	5	4.94 $\pm$ 0.47	5.00 (4.50-5.35)	0.882 +

+p-value is generated by One Way analysis of variance (ANOVA). # p-value is generated by Kruskal-Wallis test. *p-value $\leq$ 0.05 is considered statistically significant.

Ad-SOS: Amplitude dependant speed of sound. BTT: Bone transmission time. ALP: Alkaline phosphatase. 25OH(D): 25-hydroxy vitamin D.

were girls. Overall median age was 104.48 months (IQR: 77.77-128.04 months). There were 9(14.75%) children with Down's Syndrome and 18(29.52%) with CP. The cause of ID was unknown in 34(55.73%) children. According to ID grades, 18(29.5%) children had Mild ID, 38(62.3%) had Moderate ID and 5(8.2%) had Severe ID. Besides, 17 (27.9%) subjects had below-normal bone profile. The mean QUS bone profile Z-Score of all children with ID was -0.77 ± 1.29 . Mean Ad-SOS was 1809.26 ± 52.54 m/sec. Ad-SOS of children with ID having below-normal bone profile was significantly lower than children with normal bone profile ($p < 0.001$) (Table-1).

There was no significant difference between Ad-SOS of children with Mild, Moderate and Severe ID ($p = 0.170$) (Table-2). Moderate significant correlations of Ad-SOS were observed with Age (Spearman's rho = 0.470; $p < 0.001$) (Figure-1A) and ALP (Spearman's rho = -0.499,

$p < 0.001$) (Figure-1B). ALP was also significantly raised in children with ID having below-normal bone profile ($p < 0.001$).

Mean BTT of all children with ID was 0.62 ± 0.18 μ sec. BTT of children with ID having below-normal bone profile was significantly lower than that of children with normal bone profile ($p = 0.002$). No significant difference of BTT was seen between various groups of ID ($p = 0.253$).

Besides, 51(85%) children had below-normal 25OH(D) levels. Median 25OH(D) level of all children with ID was 8.59 (IQR: 5.46-17.87) ng/ml which was much less than the normal reference value of 20ng/ml.⁸ There was no significant difference between vitamin D levels of children with below-normal bone profile and that of children with normal bone profile ($p = 0.831$). Also, no significant difference of Vitamin D was seen between various groups of ID ($p = 0.387$). A mild negative correlation of 25OH(D)

was seen with age in all children (Spearman's $\rho = -0.352$; $p = 0.006$) (Figure-1C).

Discussion

Results of the present study show that considerable proportion (28%) of children with ID had below-normal bone mineral density (BMD) as assessed by QUS bone profile. Earlier studies have shown even greater proportion of children with disabilities having low BMD.^{19,20} Much less proportion of children with ID having below-normal BMD values in the present study may be explained on the basis of exclusion of children with moderate to severe motor deficits and feeding difficulties.

Significant positive correlations of Ad-SOS with age (Figure-1A) explains increase in bone mass with age in children. This finding is consistent with an earlier study²¹ on 50 children with genetic disorders, using the same instrument for QUS on phalanges as in the present study. The study sample showed slightly higher Ad-SOS value than our study sample which may be due to much younger children included in the present study.

Significantly higher levels of ALP in children with ID having poor bone profile when compared with ALP levels in children having normal bone profile as well as moderate negative correlation of ALP with Ad-SOS (Figure-1B) suggests increased osteoblastic activity resulting from progressive weakening of bones. This finding of raised ALP level in the present study's sample is consistent with numerous studies done in children with poor bone health.^{22,23}

Considerably higher proportion (85%) of children having low vitamin D levels in our study compared to previous works^{12,24} may be explained on the basis of already low levels of vitamin D in majority of normal local population as demonstrated by several studies done in Pakistan.⁹⁻¹¹ The deficiency of vitamin D in children included in our study may also be explained on the basis of limited availability of foods rich in vitamin D to this underprivileged population of children. To our knowledge, the present study is the only one showing results of vitamin D assessment specifically in children with ID from Pakistan. This extreme prevalence of vitamin D deficiency of critical level in local population of children with ID is extremely important to look at for the betterment of their bone health and can be labelled as a public health concern.

A significant mild negative correlation (Figure-1C) of vitamin D with age in all children included in the current study may be explained on the basis of greater mineral and nutrient demands of growing skeleton in children.

These results also suggest that pre-pubertal children already deficient in vitamin D status similar to our study population of ID children should be supplemented with higher levels of vitamin D with advancing age to achieve better peak bone mass and good skeletal growth.

Limitations of the current study are its small sample size and the lack of a comparison group of healthy children.

Conclusions

Significant proportion of children with ID had below-normal bone profile. Vitamin D levels were extremely low in overwhelming majority of children with ID. Significant negative correlation of age with vitamin D and positive correlation with Ad-SOS may suggest increasing requirements of vitamin D with age to cope with advancing needs of growing skeleton in children with ID.

Disclosure: The article or part of the article has not been submitted or published in any other journal.

Descriptive data regarding ultrasonographic bone profile of this study was presented as a part of poster at 165th Annual Conference of American Psychiatric Association (APA), Philadelphia, USA, 2012.

Descriptive data regarding ultrasonographic bone profile of the study was also presented as oral presentation at International Conference on Innovative Biological and Public Health Research (IBPHR-2014), Government College University, Lahore. MAY 6 - 8, 2014.

The results of this paper have been orally presented at 4th undergraduate & Postgraduate Research Symposium, CMH Lahore Medical College & Institute of Dentistry on 27th January, 2016 and 9th SAARC International Psychiatric Conference, Serena Hotel, Islamabad, Pakistan, 4th-6th March 2016.

Conflict of Interest: None.

Financial Support: The financial support by University of Health Sciences is greatly acknowledged.

References

1. Chen H, Zhou X, Fujita H, Onozuka M, Kubo KY. Age-related changes in trabecular and cortical bone microstructure. *Int J Endocrinol*. 2013;2013:213234.
2. Falk B, Bronshtein Z, Zigel L, Constantini NW, Eliakim A. Quantitative ultrasound of the tibia and radius in prepubertal and early-pubertal female athletes. *Arch Pediatr Adolesc Med*. 2003; 157:139-43.
3. Njeh CF, Boivin CM, Langton CM. The role of ultrasound in the assessment of osteoporosis: a review. *Osteoporos Int*. 1997; 7: 7-22.
4. Halaba Z, Pluskiewicz W. The assessment of development of bone mass in children by quantitative ultrasound through the proximal phalanges of the hand. *Ultrasound Med Biol*. 1997; 23:1331-5.

5. Ventura V, Mauloni M, Mura M, Paltrinieri F, de Aloysio D. Ultrasound velocity changes at the proximal phalanxes of the hand in pre-, peri- and postmenopausal women. *OsteoporosInt*. 1996; 6:368-75.
6. Guglielmi G, de Terlizzi F. Quantitative ultrasound in the assessment of osteoporosis. *Eur J Radiol*. 2009; 71:425-31.
7. Vanlint S, Nugent M, Durvasula S. Vitamin D and people with intellectual disability. *Aust Fam Physician*. 2008; 37:348-51.
8. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011; 96:53-8.
9. Qamar S, Akbani S, Shamim S, Khan G. Vitamin D levels in children with growing pains. *J Coll Physicians Surg Pak*. 2011; 21: 284-7.
10. Khan AH, Naureen G, Iqbal R, Dar FJ. Assessing the effect of dietary calcium intake and 25 OHD status on bone turnover in women in Pakistan. *Arch Osteoporos*. 2013; 8:151.
11. Iqbal R, Jafri L, Haroon A, Habib Khan A. Illuminating the dark side-vitamin D status in different localities of Karachi. *J Coll Physicians Surg Pak*. 2013; 23: 604-6.
12. Greenway A, Zacharin M. Vitamin D status of chronically ill or disabled children in Victoria. *J Paediatr Child Health*. 2003; 39: 543-7.
13. Zubillaga P, Garrido A, Mugica I, Ansa J, Zabalza R, Emparanza JI. Effect of vitamin D and calcium supplementation on bone turnover in institutionalized adults with Down's Syndrome. *Eur J Clin Nutr*. 2006; 60: 605-9.
14. Gonnelli S, Caffarelli C, Hayek J, Montagnani A, Cadirni A, Franci B, et al. Bone ultrasonography at phalanxes in patients with Rett syndrome: a 3-year longitudinal study. *Bone*. 2008; 42: 737-42.
15. Zacharin M. Current advances in bone health of disabled children. *Curr Opin Pediatr*. 2004; 16: 545-51.
16. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. *Dev Med Child Neurol*. 2008; 50: 744-50.
17. Slosson RL. (revised by Nicholson, C.L. & Hibpsham, T.H.). 1991. Slosson intelligence test for children and adults - revised. New York, Slosson Educational Publications.
18. Bluma S, Shearer M, Frohman A, Hilliard J. Portage Guide To Early Education. Wisconsin, Cooperative Educational Service Agency 5, 1976.
19. Henderson RC, Lark RK, Gurka MJ, Worley G, Fung EB, Conaway M, et al. Bone density and metabolism in children and adolescents with moderate to severe cerebral palsy. *Pediatrics*. 2002; 110: e5.
20. King W, Levin R, Schmidt R, Oestreich A, Heubi JE. Prevalence of reduced bone mass in children and adults with spastic quadriplegia. *Dev Med Child Neurol*. 2003; 45: 12-6.
21. Pluskiewicz W, Pyrkosz A, Drozdowska B, Halaba Z. Quantitative ultrasound of the hand phalanges in patients with genetic disorders: a pilot case-control study. *OsteoporosInt*. 2003; 14: 787-92.
22. Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am J Clin Nutr*. 2004; 80: 1697S-705S.
23. Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, et al. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr*. 2005; 82:477-82.
24. Vanlint S, Nugent M. Vitamin D and fractures in people with intellectual disability. *J Intellect Disabil Res* 2006; 50: 761-7.