

QUANTITATIVE ULTRASOUND BONE DENSITOMETRY IN CHILDREN WITH THALASSAEMIA IN NORTH EAST INDIA

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ABSTRACT

BACKGROUND

Thalassaemic children who are on regular blood transfusion are at increased risk of hypothyroidism, growth hormone deficiency, hypoparathyroidism, diabetes mellitus and osteoporosis because of deposition of iron in various endocrine glands with age. Low bone mineral density is a significant problem in these children, which may lead to increased risk for fractures and suboptimal peak bone mass.

The aim of the study is to determine the bone health status of children with thalassaemia using quantitative ultrasound densitometry.

MATERIALS AND METHODS

A case control study was done at Department of Paediatrics, Jorhat Medical College and Hospital, which included 32 regularly transfused thalassaemic children. Age and sex matched healthy controls were included. Quantitative ultrasound bone densitometry was done in both the groups and compared with each other.

RESULTS

Broadband Ultrasound Attenuation (BUA) and Speed of Sound (SOS) measurements were found to be independent of sex. BUA values in boys showed increasing trend with age, which was not observed in girls. SOS values did not show any increasing trend with age in both sexes. In both the groups, the BUA and SOS increased continuously with increasing age. The values of BUA were more in control group compared to case group while opposite was noticed with SOS values. BUA values were more when ferritin level was >2000 ng/dL and increased number of blood transfusion, whereas SOS values decreased with increase in serum ferritin level and number of transfusion, which was statistically significant ($P=0.0125$). Both BUA and SOS values decreased with increased severity of malnutrition, which was statistically significant for SOS ($P=0.0266$).

CONCLUSION

Quantitative ultrasound bone densitometry can be used as a screening method to assess the bone health status in children, particularly those with thalassaemia, but requires further studies in large groups.

KEYWORDS

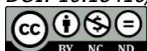
Bone Mineral Density, Broadband Ultrasound Attenuation, Quantitative Ultrasound Bone Densitometry, Speed of Sound, Thalassaemia.

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BACKGROUND

Beta thalassaemia is a disorder of haemoglobin synthesis, which is autosomal recessive in inheritance characterised by reduced synthesis of beta globin chain leading to anaemia.

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Clinical severity is variable and those with homozygous state suffer from severe anaemia for which they need regular blood transfusions.¹

Use of optimised transfusion program and chelation therapy has improved the management of these children who require regular blood transfusion. This improvement increase the life expectancy and quality of life of these patients.² But, with frequent blood transfusion, they developed new complications like iron overload resulting in deposition of iron in various organs, particularly of endocrine glands. These children are susceptible to develop hypothyroidism, growth hormone deficiency, delayed puberty, hypoparathyroidism, osteoporosis and diabetes mellitus.³

Along with the endocrine problems, they also suffer from bone problems like bone pain, growth failure, deformities, rickets, scoliosis, spinal deformities, nerve compression, pathological fracture, osteopenia and osteoporosis.²

High dose of iron chelating therapy to overcome the iron overload state may also contribute to osteopenia and osteoporosis.⁴ Transfusion dependent thalassaemia children shows a high rate of osteoporosis and osteopenia. Bone mineral density is reduced in well-transfused and well-chelated patients as well due to increased bone resorption relative to formation in them.^{5,6} There are many techniques, which are available for quantitative assessment of total bone mass and degree of osteoporosis. Bone Mineral Density (BMD) measurement by Dual Energy X-Ray Absorptiometry (DEXA) of trabecular bones such as lumbar spine, femoral neck, distal radius is considered a very reliable and noninvasive technique.^{7,8} The major disadvantage of DEXA is exposure to radiation, which is a real concern for growing children. Apart from this, the other limitation of DEXA include limited portability, lack of real-time feedback, repeatability, high cost and accessibility.⁹

In recent times, Quantitative Ultrasound Method (QUS) has emerged for evaluation of bone health and it has major advantage of lack of radiation exposure.^{10,11} Several ultrasound systems are now available and they are approved for clinical use to assess the bone density noninvasively.¹² Hologic Sahara clinical bone sonometer is one such system. In this technique, a focused wave is passed through trabecular bone such as calcaneus (heel bone) as this bone is more than 90% trabecular by volume and its BMD reflects spinal osteoporosis.^{13,14} Two parameters are important, one is Broadband Ultrasound Attenuation (BUA) and other is Speed of Sound (SOS). These two parameters provide relevant information regarding the chemistry, composition, density and structure of the underlying bone. This information cannot be provided by DEXA.¹⁵ The Sonometer system combines these two results linearly to obtain the Quantitative Ultrasound Index (QUI) and an estimate of a patient's heel Bone Mineral Density (BMD). The level of correlation between Sahara bone sonometer and DEXA heel BMD results is similar to that observed between other accepted methods for assessing BMD at the same anatomical site.¹⁶

T score which is available with this technique should not be used in children and adolescent. It compares the patients BMD with that of a healthy young adult as the child may not have achieved peak bone mass, which may lead to over prediction of osteopenia among them.¹⁷ The Z-score is a better value as it is the number of standard deviations. A patient's BMD differs from the average BMD of their age, sex and ethnicity.¹⁸ But, Z-score cannot be calculated with Hologic Sahara clinical bone Sonometer. However, to date, there are only few studies using this technique to determine the bone health status in children with thalassaemia and other haemoglobinopathies and there was no such study from this region.⁹ This study was carried out to determine the bone health status of children with thalassaemia using

quantitative ultrasound densitometer and to compare with healthy controls.

MATERIALS AND METHODS

This case control study was conducted at the Department of Paediatrics along with Department of Orthopaedics, Jorhat Medical College and Hospital, a tertiary level hospital in North East India. The primary objective was to compare the bone health status of thalassaemia patients with that of age and sex matched controls. Sample size was calculated by using OpenEpi tool. Considering a power of 80% and 95% two-sided confidence level, the sample size was calculated to be 32 in each group.

Details of the participants were recorded in a pre-structured proforma, which included age, sex, weight, height, Body Mass Index (BMI). Details like duration of disease, number of blood transfusion, serum ferritin level were recorded. Bone densitometry test was done by using Quantitative Ultrasound (QUS) method and the ultrasound scanner used in this study was Hologic Sahara Clinical Bone Sonometer, an automatic system. QUS parameters that had been assessed by the sonometer were Speed of Sound (SOS) and Broadband Ultrasound Attenuation (BUA). As T score does not have clinical utility in children and adolescent, so we did not compare T value between both groups.

Nutritional status of the cases were assessed using weight for height in children less than 6 years of age and Body Mass Index (BMI) in children more than 6 years of age and interpretation was done using WHO reference charts. Clearance from hospital ethics committee was taken. Children on regular blood transfusion were selected using the following:

Inclusion Criteria

1. Children in the age group of 2-15 years with confirmed diagnosis of thalassaemia syndrome (like transfusion dependent beta-thalassaemia, E-beta thalassaemia, thalassaemia intermedia).
2. Children with serum ferritin >1000 ng/dL, irrespective of chelation therapy.
3. Children with >10 blood transfusions.

Exclusion Criteria

1. Children on medications like antiepileptic drugs, oral calcium and vitamin D, which may affect the bone mineralisation.
2. Children with chronic use of systemic corticosteroids.

Data were analysed by MS Excel and SPSS version 23. The significance test for normally distributed variables was performed using paired t-test, unpaired t-test and ANOVA test. On the other hand, categorical data were analysed using chi-square test. P value <0.05 was considered to be statistically significant for 95% confidence interval.

RESULTS

A total of 64 subjects participated in this study, 32 in case group and 32 in healthy control group. 19 participants were boys (59.37%) and 13 participants were girls (40.62%) in

each group. Bone health status of participants was assessed using QUS parameters, i.e. Speed of Sound (SOS) expressed in meter per second (m/sec) and Broadband Ultrasound Attenuation (BUA) expressed as dB/MHz. Figure 1 shows the BUA values according to different age and sex.

BUA values in boys showed increasing trend with increase in age, which was not observed in girls. Figure 2 shows the SOS values in different age and sex. Both boys and girls did not show any increasing trend with increasing age. Table 1 shows the BUA and SOS values between cases and age and sex matched controls. In both the groups, the BUA and SOS increased continuously with increasing age. The values of BUA were more in control group compared to case group, while opposite was noticed with SOS values in different age range, although they were not statistically significant.

Table 2 shows QUS parameters according to serum ferritin level. BUA values were more (43.90±11.23) when ferritin level was >2000 ng/dL. BUA value was 42.48±10.20 when ferritin was between 1000-2000 ng/dL, whereas SOS values decreased with increase in serum ferritin level (1608.93±40.60 when ferritin was between 1000-2000 ng/dL and it was 1587.06±45.59 when ferritin was >2000 ng/dL. Table 3 shows that the BUA values increased with increase in number of blood transfusions (41.33±8.56 when number of transfusions were between 10 - <20, whereas it was 44.81±10.84 when the number of transfusions were >40) and SOS values decreased with increase in number of transfusions (1624.19±38.38 when number of transfusions were between 10 - <20, whereas it was 1594.50±48.12 when the number of transfusions were >40), which was statistically significant (P=0.0125).

Table 4 shows that BUA and SOS values decreased with increase in severity of malnutrition. BUA value was

46.41±10.59 in moderate malnutrition group and 43.87±14.25 in severe malnutrition group. SOS value was 1607.24±44.94 in moderate malnutrition group and 1599.20±51.48 in severe malnutrition group and this decrease in SOS was statistically significant (P=0.0266).

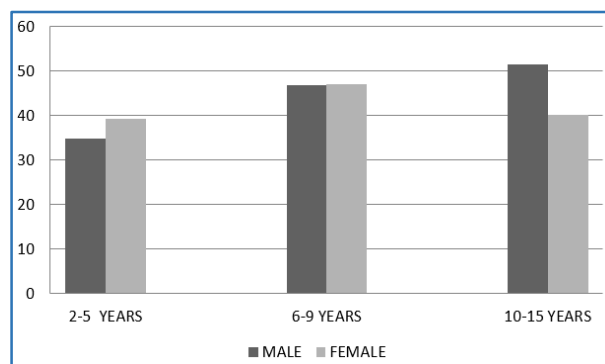


Figure 1. BUA Value (dB/MHz) in Cases According to Age and Sex

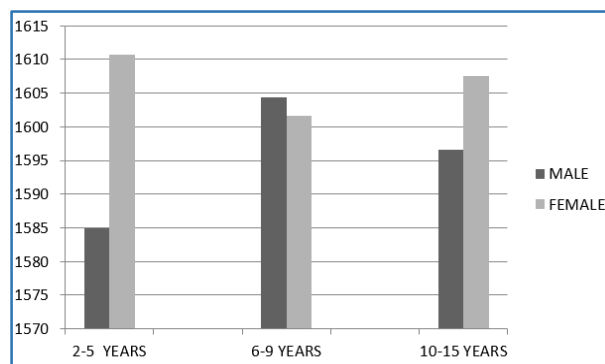


Figure 2. SOS (m/sec) Value in Cases According to Age and Sex

Age Group	BUA			SOS		
	Cases (Mean±SD)	Control (Mean±SD)	P value	Cases (Mean±SD)	Control (Mean±SD)	P value
2-5 years	36.17±8.5	39.24±5.9	0.3829	1593.56±54.3	1588.92±35.1	0.8370
6-9 years	42.93±10.9	43.89±12.2	0.4492	1603.43±31.1	1596.75±36.9	0.5722
10-15 years	43.83±8.9	54.98±11.8	0.0944	1613.85±57.2	1611.1±34.9	0.7964

Table 1. BUA and SOS Values in Cases and Control Groups

QUS Parameters	1000-2000 (20)	>2000 (12)	P value
BUA (Mean±SD)	42.48±10.20	43.90±11.23	0.7160
SOS (Mean±SD)	1608.93±40.60	1587.06±45.59	0.1690

Table 2. QUS Parameters According to Serum Ferritin (ng/dL) Level

QUS Parameters	10 - <20 (13)	21-40 (10)	>40 (9)	P value
BUA (Mean±SD)	41.33±8.56	43.56±12.87	44.81±10.84	0.5663
SOS (Mean±SD)	1624.19±38.38	1585.83±34.09	1594.50±48.12	0.0125

Table 3. QUS Parameters According to Number of Transfusion

QUS Parameters	Normal Nutrition (17)	Moderate Malnutrition (9)	Severe Malnutrition (6)	P value
BUA (Mean ± SD)	40.90±8.95	46.41±10.59	43.87±14.25	0.4045
SOS (Mean ± SD)	1597.82±41.70	1607.24±44.94	1599.20±51.48	0.0266

Table 4. QUS Parameters According to Nutritional Status

DISCUSSION

In our study, QUS parameters showed no statistically significant difference between boys and girls. Similar results were reported by other studies.^{19,20,21} Fadhli MS et al reported that BUA and SOS were independent of sex.⁹ BUA values increased with increasing age in boys, while in girls this was not observed. Mugal MZ et al reported that mean calcaneal BUA values increased between 6 and 15 years of age and boys generally had higher values than in girls.²² Fadhli MS et al in their study found that mean BUA increased with age.⁹ Wunsche K et al found a steady increase of BUA with age in both sexes.²³ In our study, BUA level in girls showed increasing trend between 2 to 9 year age group. As the thalassaemic children grow older, their bones became stronger resulting in increasing in BUA values with age.⁹ In the case and control groups, we found that the SOS and BUA values increased with increase in age in both the groups. But, when we compared the cases and control groups, we found that the SOS values were more in thalassaemic children compared to the control group, while BUA values in thalassaemic children were less than the control group. Fadhli MS et al reported similar finding in their study. They found that SOS values for thalassaemic children were higher compared to control, while the BUA values were lower in thalassaemic children compared to control indicating that the bones in these thalassaemic children were not as strong as their control who were considered to have a normal bone.⁹ This difference of BUA and SOS in two groups maybe because of difference in thickness of measured site in different age group.⁹

BUA values increased with higher serum ferritin level, while SOS values decreased with increasing level of ferritin. It maybe because of negative effect of iron overload on bone mineralisation.²⁴ The number of blood transfusion affected the BUA and SOS values. BUA values increased with increase in number of transfusions, while the SOS values decreased with increase in transfusion. This finding was in contrast to the finding of Sien PY et al who reported that there was no significant relation of SOS with frequency of transfusion.²¹ Both BUA and SOS decreased with increase in degree of malnutrition in our study. Sien PY et al did not find any significant relation among height for age, weight for age and BMI for age.²¹ The decrease in QUS values in our study maybe because of negative effects of malnutrition on bone formation. Malnourished children have low vitamin D level, which may result from either nutritional deficiency or defective hydroxylation of vitamin D in liver due to haemochromatosis as our patients had high ferritin level.^{25,26}

Regular anthropometric assessment in regularly transfused thalassaemic children is very important from clinical management point of view as we had seen from our study that QUS parameters decreased with increased severity of malnutrition. If one thalassaemic child is found to be malnourished when compared to the standard reference charts, the child maybe at increased risk of osteoporosis. In such cases, QUS assessment can be done before doing DEXA scan, which carries the risk of radiation exposure. QUS may play a vital role in deciding, which child should have a DEXA

scan. If a QUS system is available, it is preferable to have all children with thalassaemia and other haemoglobinopathies on regular transfusion to undergo screening using QUS to prevent unnecessary radiation exposure with DEXA scan, which is considered as a reference standard to measure bone density.^{9,21} There were few limitations of our study. Firstly, the small number of participants, secondly the pubertal stages using Tanners method was not assessed as QUS at calcaneus bone is influenced by growth process and additionally the diameter of the participants feet was not recorded, which may affect the results.²¹ The increasing knowledge of various QUS methods have shown that these techniques are useful to assess bone mineral status in children, particularly those with thalassaemia patients with increasing age, when the accessibility and safety of DEXA scan are considered.^{9,11}

CONCLUSION

The initial QUS parameters like BUA, SOS in particular, from calcaneus bone, can give useful information in thalassaemic children particularly those with high serum ferritin level (>1000 ng/dL), increased number of blood transfusion (>10) and those with moderate-to-severe malnutrition. But, before using this technique for assessing the bone mineral status in children, particularly those with thalassaemia, require further studies in large groups to find out the other confounding factors that may affect QUS results.

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