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ORIGINAL ARTICLE

Prospective Study

Low bone mineral density and the severity of cholestasis in biliary atresia

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Author contributions: Homchan K carried out laboratory work, collected the data, and analyzed the data; Udomsinprasert W collected blood samples and assisted in analysis of data; Chaiwatanarat T, Chongsrisawat V and Poovorawan Y examined all the patients and collected clinical data; Honsawek S designed the study, carried out laboratory work, analyzed the data, wrote the manuscript, and revised the manuscript for final submission.

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Abstract

AIM

To investigate the prevalence of osteopenia and osteoporosis in postoperative biliary atresia (BA) children and the association of bone mineral density (BMD) and biochemical parameters in postKasai BA subjects.

METHODS

A total of 70 patients with postKasai BA were enrolled in this prospective study. The patients were classified into two groups according to their jaundice status. BMD of the lumbar spine was analyzed using dual energy

X-ray absorptiometry.

RESULTS

The prevalence of low bone mass (osteopenia and osteoporosis) in BA patients were 51.4% (36 out of 70). Ten patients (35.7%) in the jaundice group and 8 patients (19.0%) in the non-jaundice group had osteopenia. Sixteen patients (57.1%) in the jaundice group and 2 patients (4.8%) in the no jaundice group had osteoporosis. In addition, lumbar spine BMD Z-score was substantially lower in the jaundice BA patients compared with non-jaundice patients. BA subjects with persistent jaundice had significantly lower serum 25-hydroxyvitamin D than those without jaundice. Further analysis revealed that lumbar spine BMD was correlated with age (r = 0.774, P < 0.001), serum albumin (r = 0.333, P = 0.005), total bilirubin (r = -0.476, P < 0.001), aspartate aminotransferase (r = -0.583, P < 0.001), alanine aminotransferase (r = -0.428, P < 0.001), and alkaline phosphatase(r = -0.456, P < 0.001).

CONCLUSION

Low BMD was associated with biochemical parameters reflecting the severity of cholestasis in postKasai BA patients.

Key words: Bone mineral density; Jaundice; Biliary atresia; Cholestasis; Severity

Core tip: Recent evidences have highlighted the importance of bone mineral density (BMD) in chronic liver disease including biliary atresia (BA). This study revealed that BA patients with persistent jaundice had significantly lower BMD and 25-hydroxyvitamin D than those without jaundice. Furthermore, lumbar spine BMD was correlated with hepatic dysfunction suggesting that low BMD was associated with outcome parameters reflecting the severity of cholestasis in postoperative BA patients.

Homchan K, Chaiwatanarat T, Udomsinprasert W, Chongsrisawat V, Poovorawan Y, Honsawek S. Low bone mineral density and the severity of cholestasis in biliary atresia. *World J Hepatol* 2017; 9(16): 746-751 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i16/746.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i16.746

INTRODUCTION

Biliary atresia (BA) is a progressive, idiopathic, necro-inflammatory process resulting in obliteration of the extrahepatic biliary tree resulting in intrahepatic cholestasis, hepatic fibrosis, biliary cirrhosis, and advanced chronic liver failure[1]. It is a rare disease, with the reported prevalence ranging from 1 in 5000 to 1 in 19000 live births[2]. It is the most common cause of neonatal jaundice for which surgery is indicated and also the most common indication for liver transplantation in children. The pathogenesis of BA has remained a mystery. Most of the causal theories include defects resulting from a viral infection or toxin exposure, defects in morphogenesis, genetic predisposition, defects in prenatal circulation and immune dysregulation[3-5].

Low bone mass is frequent in patients with chronic liver disorder including BA. Metabolic bone disease is a common disorder that can be found in patients with hepatic osteodystrophy, particularly those affected by chronic cholestasis[6,7]. Its etiology is complex and multifactorial and presents as osteopenia and osteoporosis which should be investigated and diagnosed early in patients with chronic liver disease in order to minimize the risk of fractures and improve their quality of life[8,9]. The purpose of this study was to determine bone mineral density (BMD) from postKasai BA children and to investigate the association of BMD and outcome parameters in postoperative BA patients.

MATERIALS AND METHODS

Patients

This investigation was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University and was conducted in compliance with the Declaration of Helsinki. All parents of BA children were informed of the study's objectives, and written informed consent was derived from the parents prior to the participants entering the study.

A total of 70 postKasai BA subjects (30 males and 40 females; mean age 7.6 ± 0.5 years) who attended the follow-up visit in Pediatric Liver Clinic at King Chulalongkorn Memorial Hospital were recruited in the present study. Among the 70 BA children in this study, none of them had any evidence of residual infection or ascending cholangitis or clotting abnormalities during venipuncture. None had experienced liver transplantation. To compare the clinical outcomes among BA subjects, they were allocated into two groups corresponding to their levels of serum total bilirubin (TB): Non-jaundiced group (TB < 2.0 mg/dL, n = 42) and persistently jaundiced group (TB ⩾ 2.0 mg/dL, n = 28).

Laboratory tests

Venous blood specimens were procured from each subject, centrifuged, and then kept at -80 ℃ until measurement. Liver function tests including TB, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were assessed using Hitachi 912 automated chemical analyzer at the central laboratory of our hospital. Serum 25-hydroxyvitamin D [25(OH)D] levels were analyzed using automated chemiluminescent immunoassay (Diasorin, Saluggia, Italy).

BMD assessments

Dual-energy X-ray absorptiometry scans (Hologic QDR

Table 1 Demographic data and laboratory parameters of biliary atresia patients based on status of jaundice

BA patients	Total	Jaundice	No jaundice	*P*-value
n	70	28	42	
Gender (male/female)	30:40	12:16	18:24	0.5
Age (yr)	7.6 ± 0.5	6.3 ± 0.8	8.6 ± 0.6	0.01
Albumin (g/dL)	3.9 ± 0.1	3.2 ± 0.3	4.3 ± 0.1	< 0.001
Total bilirubin (mg/dL)	3.8 ± 0.7	8.2 ± 1.5	0.9 ± 0.1	< 0.001
Direct bilirubin (mg/dL)	2.5 ± 0.6	5.8 ± 1.1	0.2 ± 0.1	< 0.001
AST (IU/L)	148.8 ± 13.7	235.9 ± 20.9	90.8 ± 11.3	< 0.001
ALT (IU/L)	133.3 ± 12.8	183.4 ± 18.4	99.8 ± 15.7	0.001
ALP (IU/L)	501.7 ± 36.3	681.6 ± 46.3	381.8 ± 43.3	< 0.001
25(OH)D (ng/mL)	25.3 ± 1.1	16.0 ± 1.8	30.1 ± 0.7	< 0.001
Lumbar BMD (g/cm^2)	0.5 ± 0.0	0.4 ± 0.0	0.6 ± 0.0	< 0.001
Lumbar BMD Z-score	-1.2 ± 0.2	-2.3 ± 0.2	-0.4 ± 0.1	< 0.001

Data are expressed as mean and SEM. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BA: Biliary atresia; BMD: Bone mineral density; 25(OH)D: 25-hydroxyvitamin D.

2000, Hologic Inc., Waltham, MA, United States) were performed on the lumbar spine (anteroposterior lumbar vertebrae L1-L4) of every subject for BMD assessments. BMD was reported as grams of mineral per square centimeter (g/cm^2) and Z-scores. Z-scores of BMD were expressed as numbers of standard deviations from the mean BMD of age matched norms. Children were categorized into normal, osteopenia, and osteoporosis based on World Health Organization (WHO) criteria. Osteoporosis was designated as a lumbar spine BMD equal to or exceeding 2.5 standard deviations (SD) below the average values (Z score $\leqslant$ -2.5). Osteopenia was designated as a lumbar spine BMD below 2.5 SD but above 1 SD under the average values (-2.5 < Z score < -1.0). Normal BMD was designated as a lumbar spine BMD equal to or below 1 SD under the average values (Z score $\geqslant$ -1.0).

Statistical analysis

Statistical analysis was performed using the statistical package for social sciences software, version 22.0 for Windows. All values are expressed as a mean ± standard error. Demographic and clinical data between groups were compared by χ^2 tests and unpaired Student's *t* tests, where appropriate. Comparisons of clinical data and biochemical markers among patients with normal, osteopenia, and osteoporosis were analyzed using one-way analysis of variance (ANOVA) with Tukey post hoc test if ANOVA showed significance. Correlations between numerical data were acquired using the Pearson correlation coefficient (*r*). A *P*-value < 0.05 indicated statistically significant.

RESULTS

Comparisons between BA subjects with and without persistent jaundice

Seventy postKasai BA patients were enrolled in this prospective study. The characteristics and laboratory parameters of BA children with persistent jaundice compared to BA children without jaundice are described in Table 1. Jaundice BA subjects had markedly lower serum albumin levels than non-jaundice BA children. On the other hand, serum bilirubin, AST, ALT, ALP were considerably higher in BA cases with jaundice than those without jaundice. Subsequent analysis demonstrated that lumbar spine BMD and serum 25-hydroxyvitamin D values of jaundice BA subjects were significantly lower than those of non-jaundice BA subjects ($P < 0.001$).

Correlation of lumbar spine BMD and outcome parameters in BA subjects

The prevalence of low bone mass (osteopenia and osteoporosis) in BA subjects were 51.4% (36 out of 70). Ten patients (35.7%) in the jaundice group and 8 patients (19.0%) in the non-jaundice group had osteopenia. Sixteen patients (57.1%) in the jaundice group and 2 patients (4.8%) in the no jaundice group had osteoporosis. Subsequently, BA patients were divided into tertiles based on the WHO criteria. The first tertile included 34 patients with BMD Z-scores from 0 to -1 (considered as normal), the second tertile included 18 patients with Z-scores from -1.0 to -2.5 (considered as osteopenia), and the third tertile included 18 patients with Z-score lower than -2.5 (considered as osteoporosis). There was no statistically significant difference in gender and age distribution among the three tertiles (Table 2). However, serum albumin, serum bilirubin, AST, ALT, serum 25(OH)D and lumbar spine BMD were significantly different between the three tertiles. Further analysis revealed that lumbar spine BMD was correlated with age ($r = 0.774$, $P < 0.001$), serum albumin ($r = 0.333$, $P = 0.005$), TB ($r = -0.476$, $P < 0.001$), AST ($r = -0.583$, $P < 0.001$), ALT ($r = -0.428$, $P < 0.001$), and ALP ($r = -0.456$, $P < 0.001$). The correlations between lumbar spine BMD, age, serum albumin, serum TB, AST, ALT, ALP are illustrated in Figure 1.

DISCUSSION

BA is a serious cholestatic liver disease in neonates. The obstruction of bile flow in BA results in worsening

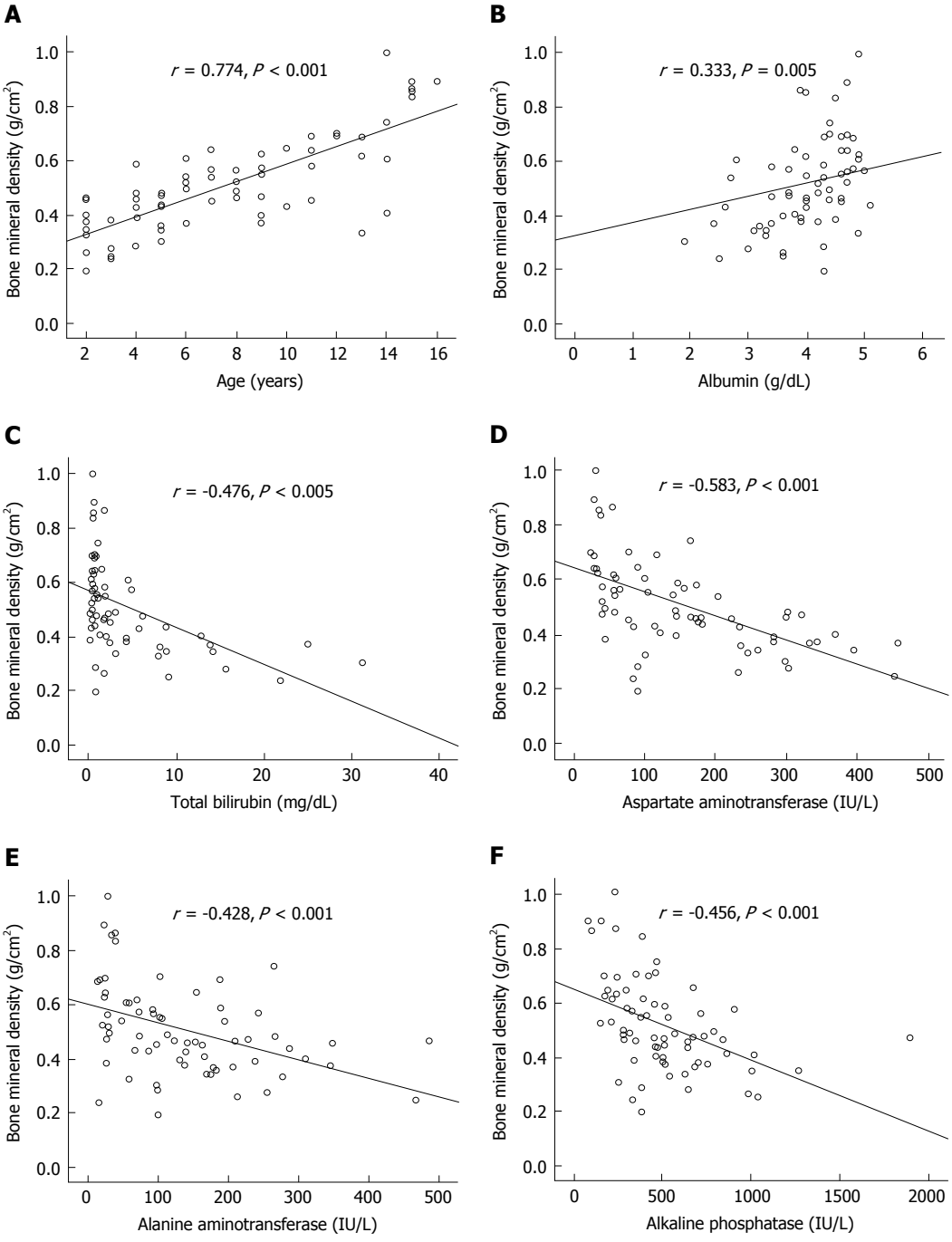

Figure 1 Scatter diagram and correlation analysis in biliary atresia patients. Lumbar spine bone mineral density are correlated with age (A), serum albumin (B), total bilirubin (C), aspartate aminotransferase (D), alanine aminotransferase (E), alkaline phosphatase (F).

cholestasis, liver fibrosis and cirrhosis, which lead to portal hypertension and eventually end-stage liver failure in children. Early diagnosis and timely Kasai porto-enterostomy to restore bile flow can help avoid the need of liver transplantation during childhood in a number of patients[10]. Despite a number of extensive clinical research studies on BA, the etiology and pathogenesis of BA are largely unknown.

In the recent years, serum 25-hydroxyvitamin D level was decreased in BA patients with low BMD[11]. Additionally, circulating leptin and osteoprotegerin levels has been shown to be correlated with BMD and the presence of jaundice in BA, suggesting that leptin and osteoprotegerin could play a pontential role in maintaining bone mass of BA patients[12,13].

The current study showed that postoperative BA patients with jaundice had significantly lower lumbar spine BMD than those without jaundice. Moreover, we have illustrated that the prevalence rates of osteopenia and osteoporosis in jaundiced BA subjects were higher in comparison with those in non-jaundiced children. Further analysis revealed an inverse association between lumbar spine BMD and serum TB and liver synthetic function. The explanation for these findings may be attributable to

Table 2 Comparison of clinical characteristics and laboratory parameters among biliary atresia patients with normal, osteopenic, and osteoporotic bone mineral density Z-scores at the lumbar spine

Characteristics	Normal	Osteopenia	Osteoporosis	*P*-value
n	34	18	18	
Gender (male/female)	15/19	7/11	8/10	0.3
Age (yr)	8.2 ± 0.7	7.7 ± 1.1	6.5 ± 1.0	0.4
Albumin (g/dL)	4.1 ± 0.2	4.0 ± 0.1	3.3 ± 0.2	< 0.05
Total bilirubin (mg/dL)	1.0 ± 0.2	2.8 ± 0.7	10.0 ± 2.1	< 0.001
Direct bilirubin (mg/dL)	0.4 ± 0.1	1.6 ± 0.5	7.3 ± 1.7	< 0.001
AST (IU/L)	95.6 ± 13.7	177.1 ± 24.8	221.2 ± 31.2	< 0.001
ALT (IU/L)	104.2 ± 18.2	164.6 ± 23.7	156.8 ± 25.1	< 0.001
ALP (IU/L)	429.1 ± 55.7	538.4 ± 55.2	602.3 ± 71.3	0.08
25(OH)D (ng/mL)	33.2 ± 0.7	26.3 ± 0.5	14.3 ± 1.5	< 0.01
Lumbar BMD (g/cm^2)	0.6 ± 0.0	0.5 ± 0.0	0.4 ± 0.0	< 0.001

Data are expressed as mean and SEM. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BA: Biliary atresia; BMD: Bone mineral density; 25(OH)D: 25-hydroxyvitamin D.

decreased osteoblastic function or increased osteoclastic resorption in BA patients. It has been documented that osteoblast proliferation was inhibited by unconjugated bilirubin *in vitro* and by the serum of jaundiced patients, indicating that bilirubin might have a direct effect on bone metabolism[14,15]. A number of BA cases eventually become advanced stage of liver disease and pediatric liver transplantation is the treatment strategy of choice for improving quality of life in BA children. Recent study has reported that successful liver transplantation could improve biochemical markers of bone formation and resorption suggesting acceleration of growth process in BA children[16]. However, the connection between cholestasis and low bone mass in BA patients merits further investigations.

Some caveats need to be acknowledged regarding the current study. First, the number of patients and controls enrolled in the present study was relative small. This could reduce the statistical power of these results. Accordingly, prospective longitudinal study with a larger population is warranted to elucidate the exact relationship between BMD, outcome parameters, and the severity in BA subjects. Secondly, inadequate measurement of plausible confounding factors including comorbidities needed to be taken under advisement. Moreover, another limitation of our study is the lack of Child-Pugh and Model for End-Stage Liver Disease (MELD) scores. Future study is also required to evaluate the Child-Pugh and MELD values for predicting of chronic liver disease severity. Ultimately, the paucity of quantitative bone histomorphometry analysis which may render evidence as to whether bone was correlated with BMD data. Therefore, more research will be needed in order to better comprehend the precise role of bone mass in the severity of postKasai BA.

To summarize, the current study demonstrated that BA subjects with persistent jaundice had significantly lower BMD than those without jaundice. Additionally, lumbar spine BMD was correlated with hepatic dysfunction suggesting that low BMD was associated with outcome parameters reflecting the severity of cholestasis in postKasai BA patients.

COMMENTS

Background

Biliary atresia (BA) is a severe congenital cholestatic liver disease with an unknown etiology. Metabolic bone disorder (osteopenia and osteoporosis) can be complicated by existing chronic liver diseases including BA. There is evidence that serum markers of bone metabolism correlated with the degree of jaundice in BA.

Research frontiers

In recent years, much research has revealed that vitamin D deficiency is associated with the severity of hepatic fibrosis or reduced bone mineral density (BMD) in patients with chronic liver disease. This study showed that lumbar spine BMD and 25-hydroxyvitamin D level in BA patients with jaundice were lower than those without jaundice. Moreover, low BMD was associated with serum bilirubin and liver function.

Innovations and breakthroughs

Jaundiced BA patients showed significantly lower lumbar spine BMD and 25-hydroxyvitamin D than in non-jaundiced BA patients. Additionally, lumbar spine BMD correlated with hepatic function markers, which reflect the severity of cholestasis in postKasai BA patients.

Applications

BMD could be used to assist clinicians in assessing the progression of cholestasis. This study highlights the need of vitamin D supplementation and its potential in maintaining bone mass in persistently jaundiced BA children.

Terminology

BMD is the amount of bone mineral per unit volume of the bone tissue and is used as an indirect parameter of bone health. BMD measurements of the patients are generally compared to those from age-matched population and are expressed as Z-score. Osteopenia is defined as Z-score between -1 and -2.5, and osteoporosis as Z-score < -2.5.

Peer-review

A very interesting study to explore the prevalence of osteopenia and osteoporosis in post-Kasai BA children and the association of bone mineral density and biochemical parameters in postoperative BA patients.

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