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IMPACT OF CHRONIC LIVER DISEASE ON BONE DENSITY IN CHILDREN: A DEXA SCAN STUDY

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ABSTRACT

Reduced bone density is a common complication of chronic liver disease (CLD) in both adults and children. Factors contributing to bone mineral deficits are dependent on the pathophysiology and severity of the underlying liver disease. This case-control study aims to assess the bone mineral density in children (4-13 years old) suffering from CLD, using a dual-energy X-ray absorptiometry (DEXA) scan. The study was conducted in the Children's Welfare Teaching Hospital (Baghdad, Iraq) from 1 November 2023 to 1 November 2024. Bone mineral density has been assessed by DEXA scan for 78 patients and controls in the pediatric age group. The mean Z-score was −0.44 among patients and 0.45 among the control group. This difference was statistically significant (p=0.02). According to the DEXA scan Z-scores, bone mineral density was significantly lower among children with CLD. Bone mineral density was correlated with alkaline phosphatase (ALP) and the duration of disease. Although there was a difference in Z-score levels across different disease types, this difference did not reach statistical significance.

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Introduction

Chronic hepatitis can be caused by persistent viral infections, drugs, metabolic diseases, fatty liver disease, or idiopathic disorders, which may have features of autoimmunity. Drugs commonly used in children that can cause chronic liver injury, which can mimic autoimmune hepatitis, include isoniazid, methyldopa, pemoline, nitrofurantoin, dantrolene, minocycline, and the sulfonamides. Metabolic diseases can lead to chronic hepatitis, including α 1-antitrypsin deficiency, inborn errors of bile acid biosynthesis, Wilson's disease, and hepatitis B and C.[1]

A decrement in bone density is a well-known complication of chronic liver disease (CLD). The physiology and severity of the underlying liver disease play an important role in bone mineral deficits. Metabolic bone disease is found in children with chronic cholestasis, end-stage liver disease, and cirrhosis of any cause.[2-4]

Since 1987, after the commercial introduction of dual energy X-ray absorptiometry (DEXA), it has become a widely available and clinically useful tool in the evaluation and management of adult bone diseases. More recently, its utilization in the pediatric population has rapidly increased.[5]

DEXA was used in children with Alagille syndrome (ALGS) who were small for age and had reduced bone mineral content for age and height, with bone mineralization positively related to the coefficient of fat absorption but not to dietary intake, indicating that patients surviving with native liver are at risk of compromised bone health.[6,7]

Materials and Methods

A case-control study for the assessment of bone density in children, involving 39 patients (4-13 years old; 19 male, 20 female) with CLDs, with a similar number of healthy children as a control group (the control group was recruited from an outpatient clinic without liver or bone diseases), was conducted in the Gastroenterology and Hepatology outpatient clinic in the Children's Welfare Teaching Hospital-Medical City Complex (Baghdad, Iraq) from November 2023 to November 2024.

Data from the control group were collected from healthy respondents through direct interviews. The interview was done through a questionnaire that comprised demographic data (age, gender, weight, height, diagnosis, and duration of the disease) and laboratory data (serum phosphate, serum calcium, serum alkaline phosphatase [ALP], and serum vitamin D level) obtained in the laboratory unit of the hospital.

DEXA scans of the lumbar vertebrae in the posterior-anterior lumbar spine (L1-L4) of the respondents were obtained using the STRATOS-DEXA-DMS machine (version v3.0.8.3, 13 January 2014, H100-130, SN G14015D365/1.0). All patients were measured using the same machine. Standard positioning techniques were used to perform the measurements. The machine is located at the Baghdad Teaching Hospital/Medical City Complex.

This study was carried out according to the guidelines of the Helsinki Declaration.[8] Patients were excluded if they had other comorbid or systemic diseases, were cognitively impaired, were bedridden, or if their parents refused to allow them to participate. In this study, Z-scores were adjusted for height.

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Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software version 23 was used for data entry and analysis. For the descriptive statistics of the socio-demographic characteristics, means, standard deviations, and minimum and maximum values were used for continuous data, while numbers and percentage values were used for countable data. An independent sample *t*-test was used to analyze the association between two continuous variables. To analyze the differences between groups, Pearson's correlation coefficient was used to determine the correlation between two continuous variables. The regression correlation coefficient was used to determine the association between laboratory findings and other variables. A p-value of less than 0.05 was used as the threshold for statistical significance.

Results

In this study, 78 children were enrolled and divided into two equal groups: the patient group (39 patients with CLDs) and the control group (39 healthy individuals matched in age and sex). The most frequent diagnosis was Wilson's disease (n=13, 33.3%), followed by autoimmune hepatitis (n=11, 28.2%) (Figure 1). The mean Z-score was −0.44 in the patient group and 0.45 in the control group, and it was significantly lower among the patient group in comparison to the control group (p=0.02) (Table 1).

In patients with CLD, the Z-score was only correlated with serum ALP and disease duration in cases where there was a significant weak negative correlation between the Z-score and ALP and disease duration (r=−0.33, p=0.03, and r=−0.4, p=0.01, respectively). No other variables had a significant correlation with the Z-score (Table 2).

The mean disease duration was 2.3±1.7 years (range from 11 months to 9 years), which is significantly correlated with the DEXA scan Z-score, as shown in Figure 2. Despite the lower Z-score among males in comparison to females, there was no significant difference in the mean Z-score between males and females across groups or within each group (Figure 3).

Also, there were differences in Z-score levels across different disease types; however, the difference did not reach statistical significance (p=0.09) (Figure 4). By running logistic regression for Z-score (dependent variable) among patients with CLD and different demographic and laboratory data (independent variables), the test showed that only disease duration was significantly associated with Z-score (p=0.02) (Table 3).

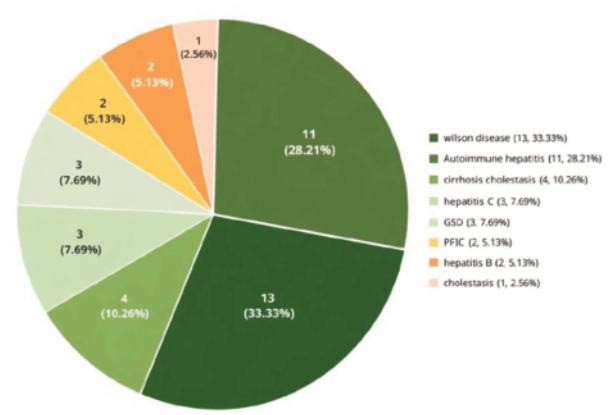

Figure 1. Distribution of CLD etiologies in the study population. GSD, glycogen storage disease; PFIC, progressive familial intrahepatic cholestasis.

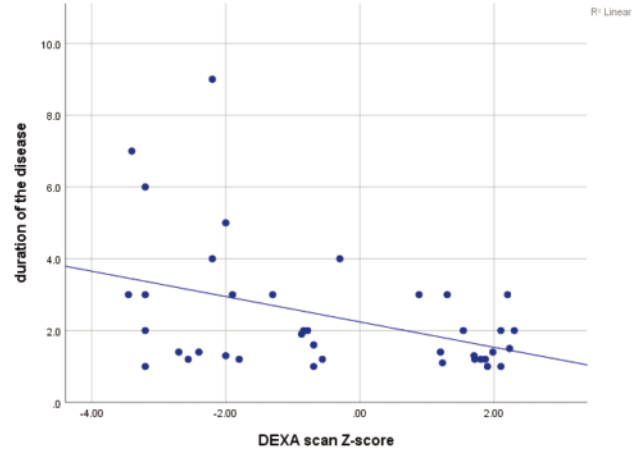

Figure 2. Correlation between disease duration and DEXA Z-score.

Table 1. Comparison of BMD (DEXA Z-score) between patients and controls.

Variable	CLD Patients	Control	p
Z-score (mean ± SD)	−0.44±2	0.45±1.4	0.028*
Low BMD (Z≤−2), n (%)	13 (33.3)	1 (2.6)	0.001**

*Independent sample t-test; **chi-square test; CLD, chronic liver disease; SD, standard deviation; BMD, bone mineral density.

Table 2. Correlation between DEXA Z-score and clinical/laboratory variables in CLD patients.

Variable	r-value	p
Age	0.1	0.52
Weight	0.18	0.26
Height	0.13	0.39
BMI	0.16	0.36
Vitamin D3	−0.085	0.6
Serum calcium	−0.05	0.73
Serum ALP	−0.33	0.03
Serum phosphorus	0.15	0.33
Duration of disease	−0.4	0.01

BMI, body mass index; ALP, alkaline phosphatase.

Table 3. Multiple linear regression analysis for predictors of DEXA Z-score in CLD patients.

Variable	β coefficient	Standard error	p
Duration of the disease	−0.440	0.191	0.028
BMI (kg/m²)	−0.118	0.635	0.854
ALP (U/L)	0.008	0.006	0.201
Serum phosphorus	−1.405	0.801	0.090
Serum calcium (mg/dL)	0.140	0.720	0.847
Vitamin D (ng/mL)	−0.058	0.045	0.203
Height (cm)	−0.039	0.168	0.817
Weight (kg)	0.125	0.349	0.722
Age (years)	0.009	0.307	0.978

BMI, body mass index; ALP, alkaline phosphatase.

Discussion

The range of pediatric age groups in our study was between 4 and 13 years old, which was comparable to the mean age of children with CLDs in a study conducted by Roy *et al.*[9] Also, in the Tahir *et al.* study, the authors found that the majority of children with CLDs were above 5 years old.[10] This means that some diseases need time to manifest their full clinical presentation of CLDs.

The gender distribution among the studied group showed a slightly higher number of females than males. This was slightly lower than the number of males in another local study by Salih *et al.*, which showed that males were 1.5 times more affected than females.[11] Also, in the previously mentioned study by Tahir *et al.*, they found that two-thirds of children with CLDs were male; although males demonstrated lower mean Z-scores compared to females, the difference was not statistically significant. This may suggest that gender does not play a major independent role in bone density in this population, although larger studies are needed to confirm this observation.

In the present study, Wilson's disease and autoimmune hepatitis were the most common etiologies of CLD. However, no statistically significant differences in Z-scores were observed across different disease categories. In contrast, a study from Egypt showed a relatively different etiology for CLD and demonstrated that chronic hepatitis was responsible for more than one-third of cases of CLD.[12]

This finding may be explained by the heterogeneity of the study population, as different liver diseases affect bone metabolism through distinct mechanisms. For instance, cholestatic disorders are primarily associated with fat-soluble vitamin malabsorption, whereas autoimmune hepatitis may impact bone density through chronic inflammation and corticosteroid therapy. The inclusion of diverse etiologies in a relatively small sample may have diluted disease-specific effects, limiting the ability to detect statistically significant differences between subgroups.

Another study by Hanif *et al.* showed that hepatitis B was the leading cause of CLD in children, followed by Wilson's disease and autoimmune liver disease,[13] while a study by Pinto *et al.* showed that biliary atresia and inherited syndromes of intrahepatic cholestasis are the most frequent causes of CLD in children.[14,15] This difference might relate to a specific age category, in which, in infants, CLDs are most often caused by biliary atresia and genetic-metabolic diseases, while in older children, they tend to result from autoimmune hepatitis, Wilson's disease, alpha-1-antitrypsin (A1AT) deficiency, primary sclerosing cholangitis, and/or the prevalence of disease in a specific country, like hepatitis.[15]

A key finding of this study is the significant negative correlation between disease duration and Z-score, suggesting that prolonged exposure to CLD is associated with progressive deterioration in bone mineral density. This finding is consistent with previous studies, including that by Loomes *et al.*, which showed that patients with CLDs had significant bone mineral deficits.[16] This observation is biologically plausible, as long-standing liver dysfunction may lead to cumulative nutritional deficiencies, persistent inflammatory activity, and prolonged metabolic derangements, all of which adversely affect bone health. Similarly, the observed negative correlation between ALP levels and Z-score may indicate increased bone turnover or underlying disease activity. However, ALP is a non-specific marker that may be influenced by hepatic and bone sources.

Despite the well-established role of vitamin D in bone metabolism, no significant association was identified between serum vitamin D levels and bone mineral density in this study. This finding may be attributed to several factors. First, bone health in CLD is influenced by multiple interacting mechanisms beyond vitamin D status alone. Second, a single measurement of serum vitamin D may not accurately reflect long-term vitamin D status or tissue-level activity. Additionally, variability in sunlight exposure, dietary intake, and supplementation among participants may have contributed to inconsistent results. These findings suggest that vitamin D alone may not be a sufficient predictor of bone mineral density in children with CLD.

Importantly, Loomes *et al.*'s study found that participants with A1AT or bile acid synthetic disorder did not have meaningful bone mineral deficits detected by DEXA, but these participants were also only mildly cholestatic at the time of the DEXA scan. In contrast, study participants with ALGS and chronic intrahepatic cholestasis had significant bone mineral deficits that correlated strongly with growth parameters. Adjustment for height and weight normalized DEXA bone mineral density and bone mineral content Z-score in ALGS, but to a lesser extent in chronic intrahepatic cholestasis. In ALGS, weight- and height-adjusted DEXA Z-scores correlated with laboratory indicators of cholestasis and hepatic synthetic function.[17,18]

In the present study, variations in DEXA Z-scores were observed across different etiologies of CLD; however, these differences did not reach statistical significance (p=0.09). This contrasts with the findings reported by Loomes *et al.*, who demonstrated significant differences in bone mineral density across specific disease subtypes. The discrepancy between the two studies may be attributed to differences in study design and population characteristics. Notably, their study included a more homogeneous and predefined set of CLD categories, allowing for clearer detection of disease-specific effects. In contrast, the present study encompassed a broader and more heterogeneous group of liver disease etiologies without prior stratification, which may have diluted potential differences and reduced the statistical power to detect significant associations.

One of the key findings from our results is that there was a correlation between the Z-score and ALP, as well as between the Z-score and the duration of the disease. However, this correlation was only significant in cases where there was a weak negative correlation between the Z-score and ALP, as well as between the Z-score and the duration of the disease. This indicates that managing CLD patients results in disease control and a decreased risk of bone density loss.[19]

From a clinical perspective, these findings emphasize the importance of routine assessment of bone health in children with CLD. Early identification of reduced bone mineral density allows for timely interventions, including nutritional optimization, vitamin supplementation, and management of underlying disease activity, which may help prevent long-term skeletal complications such as fractures and growth impairment.

Figure 3. Comparison of DEXA Z-scores between male and female participants.

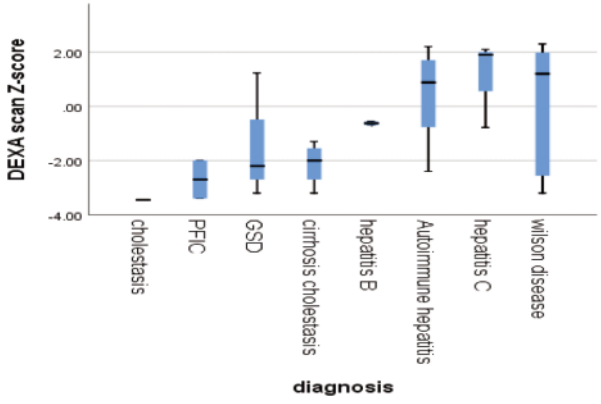

Figure 4. Distribution of DEXA Z-scores across different CLD etiologies. PFIC, progressive familial intrahepatic cholestasis; GSD, glycogen storage disease.

Conclusions

In conclusion, children with CLD are at increased risk of reduced bone mineral density, with disease duration emerging as an important contributing factor. Comprehensive and routine evaluation of bone health should be integrated into the management of pediatric CLD to enable early intervention and improve long-term outcomes.

This study has several limitations. The relatively small sample size may have limited the statistical power to detect significant associations, particularly in subgroup analyses. The cross-sectional design precludes assessment of causal relationships or longitudinal changes in bone mineral density. Additionally, the heterogeneity of liver disease etiologies may have introduced confounding effects. Important variables such as pubertal status, corticosteroid use, dietary intake, and physical activity were not evaluated and may influence bone health. Furthermore, DEXA measurements in children may be affected by growth parameters, and adjustment for height and pubertal stage was not performed.

Contributions: all authors contributed equally to the work. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflict of interest.

Ethics approval and consent to participate: the study was approved by the Ethical Scientific Committee of the Children's Welfare Teaching Hospital, and an official letter of permission from the board of pediatric medicine of the Iraqi Council for Medical Specializations was obtained. Written consent was obtained from the parents of all participants after they had been fully informed about the purpose of the study.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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