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Bone Densitometry is a Valuable Marker for Bone Health Monitoring in Pediatric Wilson's Disease Patients: A Tertiary Center Experience

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Abstract

Wilson's disease is a rare inherited disorder causing copper accumulation, which may adversely affect bone health in children. To assess bone mineral density and the prevalence of osteopenia and osteoporosis in pediatric Wilson's disease patients using DEXA. A cross-sectional study was conducted on 15 children with confirmed Wilson's disease. Bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA), and clinical, biochemical, and treatment-related variables were analyzed. The mean age was 10 ± 3.6 years; 53% were female. DEXA revealed bone disease in 60%: mild osteopenia (13%), moderate (27%), and osteoporosis (20%). Bone disease did not correlate with treatment duration, urinary copper, calcium, phosphorus, or alkaline phosphatase. However, serum albumin positively correlated with bone density ($P = .018$). Bone disease is frequent and often subclinical in pediatric Wilson's disease. DEXA is a useful tool for early detection. Larger studies are needed to evaluate the effects of treatment and micronutrient status on bone health.

Keywords

DEXA scan, bone health, Wilson's disease, pediatrics

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Introduction

Wilson disease is a rare, autosomal recessive disorder of copper metabolism characterized by hepatic, central nervous system, hematologic, renal, ophthalmologic, and cardiac complications.[1] Mutations in the ATP7B gene result in defective copper transporting P-type ATPase, primarily expressed in hepatocytes, leading to reduced synthesis of ceruloplasmin and diminished export of copper from cells. Consequently, there is progressive copper accumulation in affected organs.[2] Excess copper deposition in organs, including the brain, cornea, and kidneys, leads to free-radical cellular injury, particularly disrupting mitochondrial function in hepatocytes and impairing energy utilization.[3] Chronic copper excess induces injury, inflammation, and attempted repair, culminating in fibrosis, alongside downregulation of cholesterol synthesis, resulting in steatosis.[4] In the brain, damage and demyelination of astrocytes predominantly occur in the basal ganglia and thalamus. Additionally, excess copper in the blood leads to non-immune hemolysis, while elevated levels in the renal medulla result in renal tubulopathy.[5] Clinically, most children present with overt hepatic disease (up to 60%), whereas older children, adolescents, and adults may manifest neurologic or psychiatric symptoms. Diagnosis

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remains challenging and relies on a combination of clinical features, laboratory markers of copper accumulation, histology, and genetic analysis.[6]

It is well-established that bone health is adversely affected in patients with chronic liver disease.[7] In Wilson disease, this may be attributed to underlying hepatic osteodystrophy, chelating medications, poor nutrition, inadequate calcium and vitamin D intake, renal tubular dysfunction, reduced physical activity, and lean body mass.[8] Enhancing bone function in these patients, alongside appropriate management of Wilson's Disease, holds potential to significantly enhance their quality of life.[3] However, studies investigating bone mineral density (BMD) in this population are scarce, with data primarily extrapolated from adult literature, where approximately 50% of adult patients with Wilson disease suffer from osteoporosis and bone disease.[9] Therefore, our study aimed to explore bone mineral health, specifically osteopenia and osteoporosis, in children with Wilson Disease.

Methods

This study employed a pilot, single-center, cross-sectional descriptive design, where 15 pediatric patients aged 5 to 18 years diagnosed with Wilson's disease were recruited. Ethical approval was obtained from Kasralainy Faculty of Medicine IRB committee with approval number "MS-29-2019," ensuring adherence to the Declaration of Helsinki's ethical principles for medical research involving human subjects.

Patients with renal tubular acidosis or renal disease were excluded. Additionally, those with bilateral hip replacements, hip pins or screws, metallic rods or spinal fusion devices in the lumbar spine, recent nuclear medicine investigations with persistent radioactivity, radiological investigations utilizing contrast media, or undergoing CT scans within 1 week of the scheduled DEXA scan were excluded. Included children were either symptomatic, diagnosed based on presenting symptoms, or pre-symptomatic, identified through screening of affected index case siblings or relatives.

A comprehensive history and clinical examination focusing on the musculoskeletal system were conducted for all participants. Biochemical assessments included serum calcium, phosphorus, alkaline phosphatase, chloride, liver function tests, serum ceruloplasmin, and 24-hour urinary copper measurements. Dual Energy X-ray absorptiometry (DEXA) scans were performed at the lumbar spine to evaluate bone mineral density (BMD). BMD values were reported as *Z*-scores, indicating the standard deviations from the mean of a healthy age- and sex-matched reference population.[10] These values were compared to those of normal individuals of the same age and sex from the Radiology Department of the contributing hospital among Egyptian children. Osteopenia was defined as a *Z*-score < -2.[11]

In this study, mild osteopenia was classified as a *Z*-score between −1.01 and −1.49, moderate osteopenia as a *Z*-score between −1.50 and −1.99, advanced osteopenia as a *Z*-score between −2.00 and −2.49, and osteoporosis as a *Z*-score below −2.5 SD.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS version 20, IMB Corporation, USA). Descriptive statistics, including mean, standard deviation, median, and frequency, were utilized for data presentation as appropriate. Mann Whitney, *T*-test, Pearson Chi-square test, and Fisher's Exact test were employed where applicable to assess differences and associations. A significance level of 2-sided *P*-values $\leq .05$ was considered statistically significant.

Results

The current pilot study included 15 children diagnosed with Wilson's Disease with mean age ± standard deviation (SD) of 10 ± 3.6 years. Among them, 8 (53%) were females. Parental consanguinity was noted in 3 (20%), while 8 (53%) had another affected sibling, and a similar condition was present in the family of 9 cases (60%). At the time of enrollment in the study, the mean ± SD duration since diagnosis was 3 ± 3 years (Table 1). Eleven patients were symptomatic (73%); 3 presented with hepatosplenomegaly (20%), 3 with dystonia (20%), and 1 with tremors (7%). The median height percentile for age was 25th (interquartile range 25.3), and for weight percentile for age was 25th (interquartile range 26). At the time of enrollment and DEXA imaging, the mean ± SD ceruloplasmin level was 25 ± 17.5 mg/dL, and the mean urinary copper level was 89 ± 97.3 mg/dL range = 14-324 mg/dL. Mean hemoglobin was 12 g/dL (SD 1.45; Table 2). Liver biopsy was performed in 6 patients, with affected hepatocytes and lobules noted in 5 (83%), mild and moderate fibrosis in 2 each (33%), severe fibrosis in 1 (17%), and cirrhosis in 2 (33%; Figure 1). All patients were on copper chelation therapy, with 11 patients (73.3%) receiving oral zinc sulfate only, 4 (27%) on penicillamine, and 4 (27%) on both. The mean ± SD treatment duration was 3 ± 3.23 years.

In response to treatment, 14 (93.3%) showed a positive response to chelation therapy, with aminotransferase and bilirubin levels within normal accepted ranges, while only 1 did not, exhibiting aminotransferase levels 3 times the upper limit of normal.

Table 1. Demographic Data and Clinical Picture of Enrolled Children.

Parameter		Mean	SD
Age in years		10.3	3.5
Duration of disease in years		3.3	3.1
Sex	Females (Number, %)	8	53.3
	Males (Number, %)	7	46.7
Consanguinity		3	20
Other affected family member		9	60
Symptomatic		11	73.3
Pre-symptomatic[a]		4	26.7
Hepatomegaly		1	6.6
Hepatosplenomegaly		3	20
Dystonia		3	20
Tremors		1	6.6
Bone health	Normal	6	40
	Mild osteopenia	2	13.3
	Moderate osteopenia	4	26.7
	Osteoporosis	3	20

[a]Pre-symptomatic: diagnosed by screening of affected index case sibs/relatives. None had jaundice, ascites or liver cell failure. Mild osteopenia was defined as z-score between −1.01 and −1.49, moderate osteopenia as z-score between −1.50 and −1.99, advanced osteopenia as z-score between −2.00 and −2.49 and osteoporosis as below −2.5 SD.

Table 2. Laboratory Data of Wilson's Disease Patients.

Parameter	Normal	Mean	Standard deviation
Calcium (mg/dL)	(8.8-10)	9.49	1.35
Phosphorus (mg/dL)	(4.5-6)	6.18	4.33
Alkaline Phosphatase(U/L)	(up to 640)	348.43	270.27
Chloride (mEq/L)	(95-115)	106.00	8.49
PTH (Pg/mL)	(10-69)	48.69	25.83
Bilirubin Total (mg/dL)	(0.3-1.2)	0.61	0.38
Bilirubin Direct (mg/dL)	<0.1	0.19	0.17
Albumin (g/dL)	(3.5-5.2)	4.14	0.90
ALT (ULN)	Up to 50	1.31	1.02
AST (ULN)	Up to 40	1.69	3.43
GGT (ULN)	(4-22)	1.54	1.11
Ceruloplasmin (mg/dL)	(15-30)	24.95	17.51
Urinary copper (mg/day)	(<50)	88.99	97.31
WBCs (10^3/cm)	(4-11)	6.44	2.17
HB (gm/dL)	(12-15)	11.78	1.45
PLT (10^3/cm)	(150-450)	244.42	114.14
INR	1	1.28	0.59

Abbreviations: PTH, parathyroid hormone; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase; WBCs, white blood cells; HB, hemoglobin; PLT; platelets; INR, international normalized ratio.

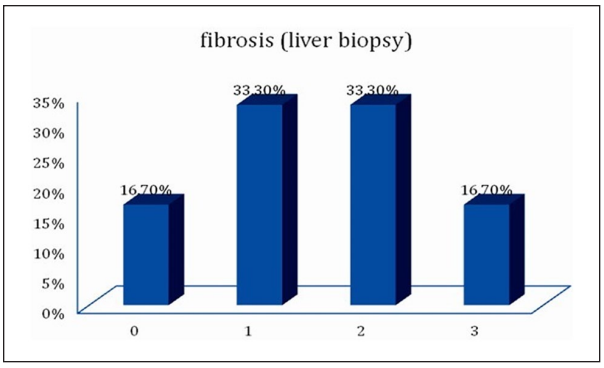

Figure 1. Liver biopsy findings in studied cases.

Table 3. Dual Energy X-Ray Absorptiometry (DEXA) Findings of Studied Patients.

Bone densitometry z score	Mean	SD	Median	Minimum	Maximum
Neck bone	−1.24	0.98	−1.10	−2.70	0.80
Lumbar spine	−1.31	0.99	−1.20	−3.00	0.70
Hip bone	−1.38	0.90	−1.40	−2.70	−0.10
Left arm	−1.19	0.92	−1.00	−2.80	0.70
Right arm	−1.25	1.03	−1.20	−2.80	0.70
Thoracic spine	−1.31	1.25	−1.20	−3.10	1.80

DEXA findings of the patients studied are shown in Table 3. Mild osteopenia was detected in 2 (13%), moderate osteopenia in 4 (27%), and osteoporosis in 3 cases (20%) while 40% had normal DEXA (Figure 2). Serum albumin correlated with bone densitometry (r=.723, P=.018). Duration of disease did not correlate with osteopenia (P=.49; Table 4). Urinary copper in 24 hours, serum calcium, phosphorus, alkaline phosphatase, and parathormone levels did not correlate with osteopenia (P=.117, P=.211, P=.237, P=.620, and P=.144, respectively). Liver biopsy findings among the 6 children with Wilson disease did not correlate with bone disease (r=.155, P=.769). No other studied parameter correlated with osteopenia.

Discussion

Wilson's disease, a rare autosomal recessive disorder, leads to systemic copper accumulation with significant hepatic and extracorporeal complications due to mutations in the ATP7B gene. Asymptomatic patients are usually discovered during family screening.[1] This disorder is not only a hepatological challenge but also involves complex systemic manifestations,[1-3] including

significant bone health issues.[7,8,12] In our study, we focused on the bone mineral health of children with Wilson's disease, an area that remains under-researched but is critically relevant given the multifactorial risks these patients face regarding bone demineralization.

Bone health in Wilson's disease is a significant concern due to the indirect effects of hepatic dysfunction and direct consequences of copper accumulation. Chronic liver diseases, including Wilson's disease, are associated with disturbed bone architecture, which can manifest as osteopenia or osteoporosis, thereby increasing the risk of fractures and affecting patients' quality of life.[7,8] Facet joint inflammation, osteomalacia, juvenile osteoarthritis, spinal osteochondritis, fractures, and heterotopic ossification have also been demonstrated in adult studies.[12] These disturbances can be attributed to a myriad of factors including malabsorption of essential minerals and vitamins due to liver dysfunction, direct bone toxicity from copper, and side effects of treatment regimens like chelation therapy, which can further deplete key bone minerals.[4]

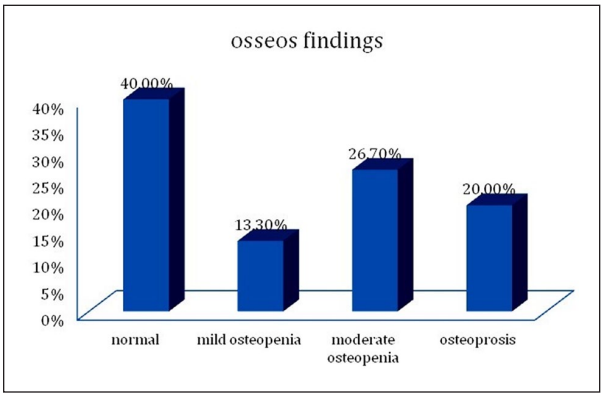

Figure 2. Distribution of Dual Energy X-ray absorptiometry (DEXA) findings of studied patients.

According to WHO definitions, osteoporosis and osteopenia are diagnosed based on *T*-scores derived from DEXA scans. A *T*-score of −1.0 or higher indicates normal bone density, while osteopenia and osteoporosis are defined by *T*-scores between −1.0 and −2.5, and below −2.5, respectively. *Z*-scores, on the other hand, compare an individual's bone mineral density with that of their peers matched for age, gender, and ethnicity. A *Z*-score of −2.5 or lower suggests a potential secondary cause of osteoporosis.[13] Previous studies have reported osteopenia and osteoporosis rates ranging from 22% to 68% among individuals with Wilson's disease.[14] Our study revealed that a substantial proportion of children with Wilson's disease suffer from decreased bone mineral density, with diagnoses of osteopenia (40%) and osteoporosis (20%) being notably prevalent. This finding aligns with existing adult studies which suggest a high frequency of bone disease in this population.[15] However, pediatric-specific data remain sparse, emphasizing the need for heightened awareness and targeted research in this subgroup.

The role of copper in metabolic processes extends to its involvement in enzymatic reactions that are crucial for maintaining bone integrity. Excessive copper, as seen in Wilson's disease, can disrupt these processes, leading to bone resorption rather than formation. This disruption is primarily mediated through oxidative stress and inflammation, which are well-documented pathways in the pathogenesis of osteoporosis.[16,17]

Furthermore, the management of Wilson's disease with chelating agents, while necessary for reducing toxic copper levels, may inadvertently affect bone density. These agents can chelate other essential minerals such as zinc and possibly influence calcium metabolism, complicating the clinical picture. Patients on long-term chelation therapy should be monitored for potential deleterious effects on bone health, and supplementation with calcium and vitamin D should be considered, especially in growing children.[18,19]

Table 4. Correlation Between Bone Densitometry and Treatment Duration.

Parameter		Neck bone densitometry (z score)	Lumbar bone densitometry (z score)	Hip bone densitometry (z score)	Left Arm bone densitometry (z score)	Right arm bone densitometry (z score)	Thoracic spine bone densitometry (z score)
Treatment duration (years)	Correlation Coefficient	−.031	.103	.026	−.059	−.057	.165
	P value	.914	.715	.927	.833	.853	.557
	N	15	15	15	15	13	15
Duration of illness (years)	Correlation Coefficient	−.190	−.084	−.152	−.055	−.057	.004
	P value	.498	.765	.588	.846	.853	.990

Additionally, reduced physical activity due to neuromuscular symptoms can contribute to lower peak bone mass in these patients. Children with Wilson's disease often experience muscle weakness, dystonia, and tremors, which can limit their physical activity, further exacerbating bone mineral loss.[20,21]

The prevalence of Wilson's disease among siblings in our study was notably higher (53%) compared to previous reports,[22] likely attributed to increased consanguinity within our community. Early detection through family screening, as demonstrated by the presence of pre-symptomatic cases in our study (27%), underscores the importance of proactive screening strategies. Given the potential for delayed onset of symptoms, annual urinary copper screening until the fifth decade among siblings of affected individuals is advisable.

The high prevalence of bone disease in our cohort, comprising mild to moderate osteopenia and osteoporosis, may reflect earlier diagnosis facilitated by familial screening. Moreover, the observed frequency could be influenced by the baseline prevalence of reduced bone density among Egyptian children, as reported in previous studies.[23] Notably, exclusion of children with renal tubular acidosis, a potential complication of Wilson's disease, from our study precludes its influence on bone density findings.[24]

Our findings revealed a positive correlation between bone densitometry and serum albumin levels, consistent with existing literature linking hypoalbuminemia to osteoporosis.[25] This underscores the importance of protein nutrition in bone health, emphasizing the multifaceted role of albumin in physiological processes. Nutritional management strategies for Wilson's disease should thus encompass dietary considerations aimed at promoting optimal bone and muscle development.

Interestingly, serum calcium levels did not correlate with bone densitometry in our study. While calcium plays a crucial role in bone health, its serum levels may not accurately reflect bone reserves, given its tightly regulated intracellular dynamics.[26] Furthermore, the absence of vitamin D & Magnesium assessments, along with the cross sectional design of the study with lack of follow-up data to evaluate the effects of specific treatment interventions—such as zinc or D-penicillamine—on bone mineral density over time, limit insights into their potential contribution to bone density alterations.

Early intervention and regular monitoring probably using DEXA scans can play a crucial role in managing bone health in pediatric Wilson's disease patients.[12,27] DEXA scans use a low dose of ionizing radiation to measure bone density as compared to other radiological procedures. A single DEXA scan usually involves a radiation dose of about 0.001 to 0.01 mSv (millisieverts). The risk of developing cancer from such low doses is minimal. In fact, the benefits of detecting bone health issues early usually outweigh the potential risks associated with radiation.[28] However, it's always an important area of research to find another more safe marker to follow up bone health, especially in populations requiring regular monitoring.

Yearly DEXA scans are generally considered safe if medically indicated (28), this approach not only aids in early detection and management of osteopenia and osteoporosis but also provides a baseline for longitudinal studies to assess the impact of various treatments on bone density.

Limitations of the Study

The current study is a pilot, single-center investigation involving a relatively small cohort of 15 pediatric patients diagnosed with Wilson's disease, which highlights the need for larger, multicenter studies to confirm these observations.

Additionally, the study did not include a control group—either healthy children or those with other chronic liver diseases—which would have provided a clearer comparison to isolate the specific impact of Wilson's disease on bone health. Instead, we utilized age- and sex-matched *Z*-scores from established normative data for Egyptian children, which serve as a validated reference for assessing bone mineral density.

It is also important to emphasize that, given the cross-sectional design of this study, our findings demonstrate associations rather than causation between Wilson's disease and bone mineral density impairments. Moreover, the study's cross-sectional design precluded assessment of longitudinal changes in bone mineral density or treatment response. The lack of follow-up data limits our ability to evaluate the potential protective or adverse effects of specific therapies such as zinc or D-penicillamine on bone health.

Conclusions

Bone disease represents a common yet under-recognized manifestation of Wilson's disease in the pediatric population. DEXA scanning proves to be a valuable and non-invasive tool for detecting subclinical osteopenia and osteoporosis in these patients. Despite the limitations of our pilot study, the findings highlight the importance of bone health monitoring in children with Wilson's disease. Future studies should aim to include larger, multicenter cohorts and appropriately matched control groups to validate and expand upon these initial observations. Additionally, ongoing research should explore the roles of vitamin D, calcium, and other micronutrient supplementation as part of comprehensive disease management strategies.

Recommendations

We recommend annual follow-up DEXA scans for pediatric patients with Wilson's disease to enable early identification and proactive management of osteopenia and osteoporosis—conditions shown to be associated with Wilson's disease in a significant proportion of patients.

Moreover, to strengthen the clinical applicability and clinical significance of our findings, future research should aim to include larger multicenter cohorts with appropriate control populations, ideally including healthy children and those with other chronic liver conditions. These studies should also assess the roles of additional bone-related micronutrients (eg, vitamin D, magnesium, phosphate) and specific treatment modalities (eg, zinc, D-penicillamine) on bone health outcomes in patients with Wilson's disease.

Authors' Note

Mayada Y. Abd EL Khalek is now affiliated to El Galaa Teaching Hospital, Cairo, Egypt.

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Abbreviations

- **DEXA**: Dual-Energy X-ray Absorptiometry
- **SD**: Standard Deviation
- **BMD**: Bone Mineral Density

Here is a list of abbreviations used in the provided text:

- **CT**: Computed Tomography
- **SD**: Standard Deviation

**SPSS: Statistical Package for the Social Sciences
mSv: Millisievert
WHO: World Health Organization

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Ethical Considerations

The study was approved by the research and ethical committee of Kasraliny Faculty of Medicine, Cairo University, Egypt, MS-29-2019.

Consent to Participate

All parents of enrolled children signed written informed consents for their children's participation in the current study.

Consent for Publication

All parents of enrolled children signed written informed consent for publication of the current study.

Author Contributions

MK, SF: set the idea of the study and designed the study. SF, HA, MA, CB: collected patients' data. MK: critically analyzed the data. MK, NK, JA, MO, SA: reviewed literature, drafted the manuscript, and wrote the final version of the manuscript. All authors reviewed and approved the manuscript for final publication.

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Declaration of Conflicting Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

All data and materials related to the study are included in the current manuscript.

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