Bone Mineral Densitometry is Recommended in Pre-liver Transplant Evaluation in Children Suffering from Wilson Disease

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ABSTRACT

Background: Wilson disease (WD) is an autosomal recessive disorder of copper metabolism with an estimated prevalence of 1 in 30,000. Osteoarticular manifestations are common feature of WD and mainly involve osteopenia, osteoporosis, and arthropathy.

Objective: This study aimed to investigate the prevalence of abnormal mineral density in a group of children with WD and evaluate if it is rational to recommend screening in pre-transplantation workups.

Methods: This study included all the children with a confirmed diagnosis of WD, followed at Nemazee Hospital affiliated with Shiraz University of Medical Sciences between 2016 and 2018. The researchers also excluded patients with other underlying diseases, abnormalities of calcium, phosphorus, or vitamin D, or those who used other medications leading to osteoporosis. Bone mineral content (BMC)/Bone mineral density (BMD) of the lumbar spine (LS-BMD) was performed for all included patients with DXA scans.

Results: Evaluation of z-scores showed osteopenia in 40% and osteoporosis in 53.33% of the patients. There was no significant association between the z-score values and cirrhosis in WD patients (P=0.559). There was a significant correlation between the value of z-scores with weight (P=0.007) and BMI (P=0.001) in patients with WD.

Conclusion: The results suggest that WD is intrinsically associated with osteoporosis. Also, patients with WD are at risk of osteopenia and osteoporosis, and screening for evaluation of bone mineral density and prophylactic supplementation may be logical, especially for those who are candidates for liver transplant due to the probability of deterioration of osteopathy in the first few months after liver transplantation.

KEYWORDS: Wilson disease; Osteopenia; Osteoporosis, Liver transplant; Bone mineral densitometry

INTRODUCTION

Wilson disease (WD) is an inherited disorder caused by mutations in the ATP7B gene [1]. The ATP7B gene encodes a plasma membrane copper-transport protein that exports copper from the cells [2]. Defects of this gene prevent the transport protein from functioning properly. As a result, copper accumulates to toxic levels that can damage the tissues and organs [3]. The main symptoms of WD are liver disease, Kayser-Fleischer rings, Central Nervous System (CNS), and psychiatric problems [4]. Osteopenia and osteoporosis are frequently seen in WD patients [5]. Osteopenia can cause a

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Table 1: Evaluation of the correlation between BMD, BMC, LS-BMD z-score, and demographic data.

		Correlations				
		Gender	**Age**	**Height**	**BMI**	**Weight**
BMD	Pearson Correlation	0.212	-0.262	-0.394*	0.580**	-0.005
	P-value	0.252	0.155	0.029a	0.001a	0.978
BMC	Pearson Correlation	-.362*	0.579**	0.581**	0.309	0.634**
	P-value	.045a	.001a	.001a	.091	0.0001a
LS-BMD z-scores	Pearson Correlation	-.097	0.170	0.329	0.481**	0.572**
	Sig. (2-tailed)	0.611	0.368	0.076	0.007a	0.001a

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
[a]Significant correlation
BMD: Bone mineral density
BMC: Bone mineral content
LS-BMD: Lumbar spine bone mineral density

bone fracture as the first manifestation of WD [6]. Osteoporosis defined as low bone mineral density can occur due to the presence of underlying diseases such as WD [7]. Osteoporosis may result from chronic liver disease due to low bone turnover with reduced osteoblast function [8]. Evaluation of lumbar spine bone mineral density (LS-BMD) using dual-energy x-ray absorptiometry (DXA) is used to classify osteopenia and osteoporosis in children with WD [9]. LS-BMD z-scores are adjusted for sex and chronological age [10]. Osteopenia and osteoporosis are defined as the LS-BMD z-scores between -1.0 to -2.5 SD and < -2.5 SD below the reference range, respectively [11]. Few studies have assessed osteopenia and osteoporosis in children with WD by measuring LS-BMD z-scores [12]. Some of the patients with WD need liver transplantation as treatment. There is evidence of bone loss after transplantation[13]. This research aimed to assess the prevalence of abnormal bone densitometry in a group of children with WD, compared to age- and gender-matched normal references and evaluate if it is rational to recommend BMD as pre-transplant evaluation.

MATERIALS AND METHODS

This is a cross-sectional study conducted on children with a confirmed diagnosis of WD followed at Nemazee Hospital affiliated with Shiraz University of Medical Sciences between 2016 and 2018. Exclusion criteria were either the presence of other underlying diseases such as diabetes or thyroid dysfunction, any abnormalities of calcium, phosphorus, or vitamin D, or the consumption of medications causing bone demineralization. The unwilling patients were also excluded. All the eligible patients enrolled in the study had received their care at the study center. Data on associated problems of disease manifestations (presence or absence of cirrhosis at diagnosis or at time of BMD measurement), medications, and laboratory results were collected, and written informed consent was obtained. In children below the age of 5, it is possible to measure the bone mineral content and bone mineral density in the spine. However, performing whole-body measurements is only feasible for children aged 3 years and older. It should also be noted that in younger patients, particularly those below 13 years of age, the reliability of dual-energy X-ray absorptiometry measurements in the hip region is limited[14]. So, in our study, we measured on spine. LS-BMD was performed with the Hologic Dual Energy X-Ray Absorptiometer (DXA Hologic discovery wi, Waltham, MA), APEX system software version 3.3, and the Low-Density Spine Option was used for all patients under 12 years of age. DXA scan results were normalized to z-scores based on comparisons to age- and sex-specific normative values provided with the Hologic discovery wi software. According

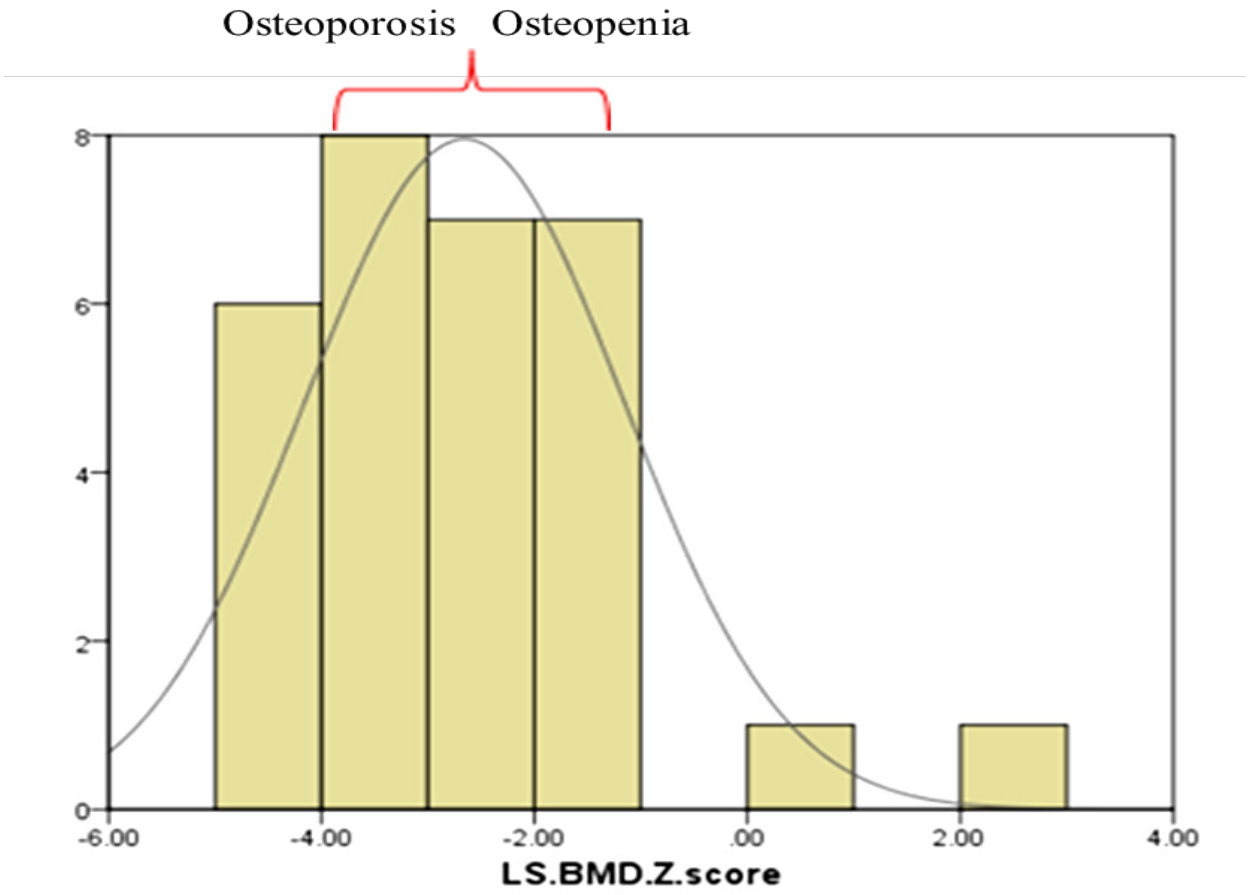

Figure 1: The distribution of LS-BMD z-scores in WD patients.

to the WHO definition, osteopenia is defined by a z-score ranging from -1 to -2.5, whereas values below -2.5 indicate a diagnosis of osteoporosis. [15] Height and weight were measured by digital balance and stadiometer and obtained on the day the subjects underwent DXA. Body mass index (BMI) is a commonly used index that utilizes an individual 's weight and height to estimate their body fat, for age and gender. BMI categories are determined based on specific percentiles that take into account sex and age. Healthy weight is defined as BMI between the 5th percentile and less than the 85th percentile. A low BMI is defined as lower than the 5th percentile while a higher BMI is more than the 85th percentile.

Ethical Considerations

The ethics code for this project was IR.SUMS.MED.REC.1398.317.

RESULTS

This study included 31 patients with Wilson's disease. 61.3% of the cases were boys and 38.7% were girls. The mean age of the patients was 13.55 ± 3.778 years. The average height and weight of the patients were 154.048 ± 21.257 cm and 48.316 ± 19.086 kg, respectively. The BMI values were lower than the normal range in 21.05% of boys and one of the girls. However, 10.52% of the boys and one of the girls had higher BMI than their age normal range. Liver cirrhosis and Kayser–Fleischer rings were observed in 58.06% and 25.32% of patients, respectively.

The mean BMD was 1.10 ± 1.917 g/cm2. There was no significant difference between the mean BMD in boys and girls (P-value = 0.252). According to Pearson's correlation coefficient, there was a significant correlation between BMD and height, and BMI. BMD

was higher in taller patients and those with higher BMI. The mean bone mineral content (BMC) was 1091.19 ± 707.665 g/cm. BMC was calculated by the sum of the BMD values over the projected area. Mean LS-BMD z-scores were -2.657 ± 1.504. The minimum and maximum amount of LS-BMD z-scores in the patients was -4.88 and 2.30, respectively. However, mean LS-BMD z-scores in girls (-2.83 ± 1.083) were higher than boys (-2.5minus 1.751. There was no significant difference between the mean LS-BMD z-scores in boys and girls (P-value = 0.611). The prevalence of osteopenia and osteoporosis in the studied population was 40% and 53.33%, respectively. The incidence of osteopenia and osteoporosis was higher in females (41.66% and 58.33%) than in males (33.33% and 55.56%). The LS-BMD z-scores distribution in WD patients are shown by a histogram (Fig. 1).

However, there was no significant correlation between LS-BMD z-scores and laboratory data. There was a significant relationship between LS-BMD z-scores and high weight and high BMI. The results of Pearson's correlation coefficient test are shown in Table 1.

DISCUSSION

WD is a hereditary disorder in copper metabolism that can lead to multiple clinical manifestations [5]. The bone manifestations, mainly osteopenia, and osteoporosis, are a common feature in patients with WD [16]. In the present study, we investigated 31 children with WD in which the prevalence of osteopenia and osteoporosis was 40% and 53.33%, respectively. To the best of our knowledge, there were only two studies that had quantified BMD in children with WD [17]. Selimoglu et al. studied 31 children diagnosed with WD. They reported the prevalence of osteopenia and osteoporosis in children with WD to be 22.6% and 67.7%, respectively [17]. In both studies, the severity of the disease did not affect the LS-BMD z-scores. Cetinkaya et al. measured BMC and BMD by DXA in 27 children with WD. They reported no significant difference between the mean BMC and BMD values in patients and healthy controls [18]. Quemeneur et al. assessed BMD in 85 adult patients with WD. The mean BMD was normal in their studied population. However, 14% of the cases suffered from osteoporotic fractures [19]. In another research, Hegedus et al. studied 21 patients with WD with a mean age of 30.8 years and the age range of 14–46 years. They reported osteoporosis in 43% of patients with WD [20]. According to a large cohort study, (115 patients with WD) published in 2015 by Weiss et al., 58.8% of the studied cases with WD had lower LS-BMD z-scores than their matched normal controls. 50% of the patients showed osteopenia and 8.8% osteoporosis [12]. A systematic review estimated the prevalence of osteopenia and osteoporosis at 50.0% and 17.6%, respectively. This study suggested that young age and male status correlated with higher osteoporosis prevalence in WD patients [21]. However, we did not find any significant correlation between LS-BMD z-scores and age and gender in our studied population. Kalra et al. studied the clinical presentations of 25 children with WD. They reported only one patient with osteopenia. However, they did not analyze BMD and considered osteopenia as medicine adverse effects [22]. Shin et al. reported a 25-year-old male with no previous history of any diseases who experienced a slip-down injury while walking. They found osteopenia while evaluating the bone quality, and laboratory findings led to the diagnosis of WD in this patient [6]. Accordingly, bone manifestation can be the only clinical manifestation of WD. However, the prevalence of osteopenia and osteoporosis is high in patients with WD; it can be due to liver cirrhosis. Chronic liver disease and cirrhosis can increase the risk of osteopenia and osteoporosis [23]. In the present study, 58.06% of the patients with WD had liver cirrhosis. On the other hand, some patients took medications such as Calcium, Vitamin D, and Rocaltrol, which can decrease the risk of osteoporosis [24]. Accordingly, osteopenia and osteoporosis may not be diagnosed in some patients with WD.

Post-transplantation bone loss is a concern for pediatricians. There is evidence of bone loss

in the first 3 months after liver transplantation and an increase in fractures in the first 6 months [13]. On the follow-up of 360 post-transplant patients, 82% had bone loss in the first 4 months after transplantation[25]. On the long-term follow-up of pediatric patients who underwent a liver transplant, Guthery et al. demonstrated that 7.3% of patients had bone loss [26]. There is also 5 times more probability of osteoporosis in post-liver transplant recipients compared to non-transplant ones [27]. Pretransplant osteopenia and osteoporosis are the major risk factors for post-transplant fractures [27]. Sharma et al. demonstrated the association of low BMD with post-transplant mortality and the outcome of patients with hepatocellular carcinoma [28]. Younger age and male sex are associated with more prevalence of osteoporosis in patients with Wilson disease [29]. Guichelaar et al. also demonstrates that younger age is a risk factor for posttransplant bone loss [25].

Immunosuppressive therapy accounts for the aggravation of osteopathy in post-transplant patients [25, 30]. The mechanisms for cyclosporin, an immunosuppressive drug, that are attributed to bone loss are high bone turnover, downregulation of renal calbindin RNA, and impairment of testosterone production [31, 32]. The mechanism of glucocorticoids which induce decreased BMD is the cessation of osteoblastogenesis and induces apoptosis of osteoblasts and osteocytes [33]. The role of glucocorticoids for BMD in post-transplant patients is controversial. Nightingala et al. found no correlation between corticosteroid exposure and BMD in post liver transplant patients [34]. Scolapio et al. reported no effect of corticosteroid use beyond 4 months on BMD in patients who have undergone liver transplantation [35]. Some reports suggest the lower dose and shorter duration of glucocorticoid to decrease low BMD [36, 37]. The increase in BMD was seen by tapering and discontinuing glucocorticoid [35, 38].

Overall, given the risk factors of post-transplant bone loss such as younger age, glucocorticoid medication, immunosuppressive therapy which is inevitable, and pretransplant osteopathy, the importance of low BMD that may be attributed to the outcome and mortality of post-transplant patients, and the high prevalence of osteopathy in WD, we recommend screening of osteoporosis on pre-operation evaluation of pediatric patients with WD, as Guthery et al. also suggest screening for pediatrics [26].

The limitations of our study were the population size; we suggest that further studies should be conducted in the multicenter study and larger population. Patients may benefit from treatment of osteopathies before liver transplant, so it should be considered in further studies as it may affect post-transplant outcome.

In conclusion, osteoporosis and osteopenia are common manifestations in patients with WD. We recommend BMD measurement and proper treatment as soon as WD is diagnosed. Screening for evaluation of bone mineral density and prophylactic supplementation may be logical, especially for those who are candidates for liver transplant.

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