

Original paper

Prevalence and predictors of post-liver transplantation metabolic bone diseases

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Abstract

Introduction: Post-liver transplantation (LTx) bone diseases have been poorly investigated. The frequency of bone diseases (osteopenia and osteoporosis) after LTx is unknown.

Aim of the study: To define prevalence and risk factors of bone disorders following LTx.

Material and methods: This prospective study was conducted on 100 consecutive adult patients who underwent living donor liver transplantation (LDLT) at the National Liver Institute (NLI) and survived longer than a year. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorption (DEXA), as well as other pre- and postoperative risk factors.

Results: The frequencies of osteopenia and osteoporosis were found to be 14% and 8% among post-LTx patients. Seven recipients of the osteoporotic group were males, with mean age, and body mass index (BMI) before and after LTx 49.5 ± 7.4 years, 24.1 ± 4.7 kg/m² and 22.8 ± 1.5 kg/m², respectively. A significant association between hepatitis C virus (HCV)-related cirrhosis, liver disease severity according to Child-Turcotte-Pugh (CTP) score, and alcoholism with decreased post-LTx BMD was substantiated ($p < 0.05$, 0.006). Post-LTx development of diabetes mellitus (DM), weight gain, use of corticosteroids and basiliximab all significantly affected decreased post-LTx BMD ($p < 0.05$). However, binary regression revealed that post-LTx occurrence of DM ($p = 0.012$, odds ratio [OR] = 0.099), the severity of liver disease ($p = 0.023$, OR = 0.217), and HCV ($p = 0.011$, OR = 0.173) are the main independent predictors of metabolic bone disease (MBD) occurrence one year after LTx.

Conclusions: Post-LTx bone disorders are not infrequent complications and should be more considered in those with HCV-related severe liver disease or developed DM after LTx.

Key words: post-liver transplantation, bone disease, osteoporosis, osteopenia.

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Introduction

Liver transplantation (LTx) is the most curative therapy for end-stage cirrhosis of all etiologies. It has improved the life quality and expectancy of patients with end-stage liver disease [1]. However, both patients and physicians should be aware of the postoperative complications, which might be deleterious. With the longer achieved post-LTx survival, the incidence

of metabolic disorders had increased [2]. Multiple factors have been incriminated in the pathogenesis of bone loss after transplantation [3]. Unconjugated bilirubin was reported to cumulatively enhance osteoblast proliferation. The well-defined insulin-like growth factor-1 (IGF-1) reduction in advanced cirrhosis had deterred bone remodeling and maintenance [4]. Additionally, post-menopausal hypogonadism might trigger the condition in females [5]. Moreover, deficiency

of vitamin D in advanced liver disease might significantly affect the health of bones [6]. Other underrated risk factors including smoking, physical inactivity, alcohol consumption, older age, and low body mass index (BMI) have also been incriminated [7]. Corticosteroid use, common after transplantation and in patients with autoimmune liver disease, was reported to increase the risk not only of osteoporosis but also of avascular necrosis [8]. The adverse effects of glucocorticoids (GCs) and calcineurin inhibitors (CNIs) on bone remodeling have been reported [9]. The cumulative effects of advanced liver disease on bone osteodystrophy have been defined as an attribute [10]. Since some of these variables might be modifiable, identifying vulnerable groups is of importance. Accordingly, this study aimed to define the frequency of metabolic bone diseases (osteopenia and osteoporosis) after LTx by recruiting recipients who had undergone bone mineral density (BMD) measurement by DEXA, as well as the associated pre-operative and postoperative risk factors.

Material and methods

This observational prospective hospital-based study was conducted on one hundred consecutive adult patients (age ≥ 18 years) who underwent LDLT in the National Liver Institute, Menoufia University (NLI), and survived longer than one year. Enrolled cases were observed before, intra-operatively, and after liver transplantation with follow-up for at least one year (Fig. 1).

Donors were evaluated according to the NLI protocol (Kyoto University) [11].

Recipients were subjected to the following:

1. Informed consent: All enrolled patients had signed informed consent. The study was carried out according to good clinical practice (GCP) and the Helsinki Declaration of 1975 [12].
2. Calculation of BMI (kg/m^2): $\text{BMI} = \text{kg}/\text{m}^2$ where kg is a person's weight in kilograms and m^2 is their height in meters squared. A BMI of 25.0 or more is overweight, while the healthy range is 18.5 to 24.9. BMI applies to most adults aged 18-65 years.
3. Laboratory investigations (at post-transplantation discharge, 3 months, 6 months and one year after LTx): liver function tests (transaminases, albumin, alkaline phosphatase, γ -glutamyl transferase), complete blood count, renal function tests (urea, creatinine, uric acid, Na and K).
4. Diagnosis of diabetes mellitus (DM) according to the 2016 American Diabetes Association (ADA) criteria (2016): fasting plasma glucose (FPG) ≥ 126 mg/dl,

or 2-h plasma glucose (PG) ≥ 200 mg/dl, or $A_{1c} \geq 6.5\%$, or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥ 200 mg/dl.

5. Calculation of Model of End-Stage Liver Disease (MELD): according to the following formula: $\text{MELD} = 3.78 \times \ln [\text{serum bilirubin (mg/dl)}] + 11.2 \times \ln [\text{INR}] + 9.57 \times \ln [\text{serum creatinine (mg/dl)}] + 6.43$.
6. BMD measured by dual-energy X-ray absorption (DEXA): For all patients (once) one-year after LTx. The WHO has defined osteoporosis as a T-score of less than or equal to -2.5 and osteopenia as a T-score between -1.0 and -2.5 . BMD is measured at both the spine and hip [13, 14]. Baseline BMD was not included in the study as it is not a routine pre-transplantation test according to the Kyoto University protocol.

Statistical analysis

Data were collected and entered into the computer using the SPSS program for statistical analysis. Quantitative data are shown as mean (M), standard deviation (SD), and range. Qualitative data are expressed as frequency and percent at the 95% confidence interval (95% CI). A χ^2 test was used to measure the association between qualitative variables. Student's *t*-test was used to compare means and standard deviations of two sets of quantitative normally and non-normally distributed data respectively. A logistic stepwise regression model

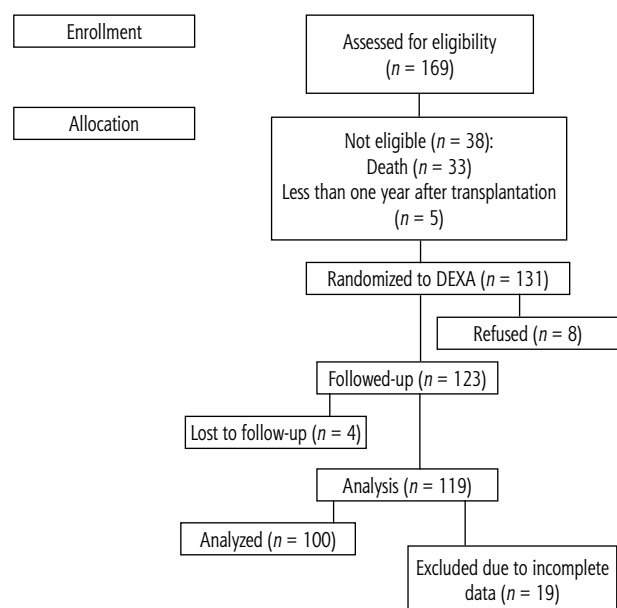


Fig. 1. Consort graph illustrating enrollment steps

was used to give an adjusted OR and 95% CI of the effect of the different independent and dependent risk factors for bony metabolic complications after liver transplantation. Two-tailed p (probability) values were considered statistically significant if less than 0.05.

Results

The frequencies of osteopenia and osteoporosis were found to be 14% and 8% among patients after LTx (Fig. 2). Seven recipients of the osteoporotic group were male. The mean values of age, and BMI before and after LTx in this group were 49.5 ± 7.4 years, 24.1 ± 4.7 kg/m² and 22.8 ± 1.5 kg/m², respectively (Tables 1 and 2).

A significant association was found between liver disease severity according to CTP score at the time of LTx and post-LTx MBD. In the osteoporotic group, 3 recipients were Child B, and 5 recipients were Child C ($p < 0.05$, 0.006). Alcoholism also was significantly linked to decreased bone mass ($p < 0.05$, 0.000) (Table 1).

The most common cause of cirrhosis in the osteoporosis patients was HCV in 5 recipients with a significant difference with the other two groups ($p < 0.05$, 0.000) (Table 1).

A significant difference was detected between those with and without bone disease regarding post-LTx development of DM and weight gain ($p < 0.05$, 0.028 and $p < 0.05$, 0.004) (Table 2).

The relation between immunosuppressive drugs and osteoporosis was found to be significant in post-LTx BD for both basiliximab ($p < 0.05$, 0.019) and pulse steroid therapy ($p < 0.05$, 0.000) (Table 3).

The binary logistic regression revealed that post-LTx occurrence of DM ($p = 0.012$, OR = 0.099), the severity of liver disease ($p = 0.023$, OR = 0.217), and HCV ($p = 0.011$, OR = 0.173) are the primary independent predictors of MBD occurrence one year after LTx (Table 4).

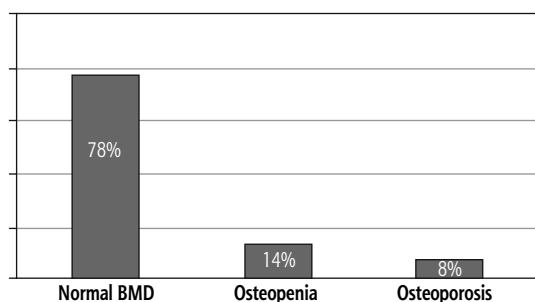


Fig. 2. Frequency of osteopenia and osteoporosis after transplantation

Discussion

Metabolic bone diseases are not an infrequent presentation of liver transplantation. A collaboration of multiple factors including liver cirrhosis per se might be incriminated in the evolution of this disorder. Bone disorders especially if associated with higher frequencies of fractures have major impacts on health-related quality of life after LTx.

In the current study on Egyptian liver transplanted patients, evaluation of post-LTx bone disorders distinguished bone mass reduction in 22% of subjects: 14% with a low bone mass (osteopenia) and 8% with osteoporosis after a minimum follow-up of one year after LTx. However, no fractures were reported at any stage of follow-up. The sunny climate in Egypt might be responsible for the relatively good bone health in Egyptians, with lower fracture rates despite the presence of osteopenia.

Females with MBD represented 44.4%, while only 19.8% of the males in the cohort were affected. This reported higher occurrence in females than males could be attributed to the age-related osteoporosis due to loss of endocrine reserve. Another additional factor might be the lack of direct sun exposure for females as they always wear the Islamic veil outdoors.

In a similar vein were the results of Isoniemi *et al.* and Giannini *et al.*, who reported that osteoporosis was found among 25% to 50% of women receiving a liver transplant [13, 14]. Fahrleitner *et al.*, in a cross-sectional study, investigated 15 patients (10 male, 5 female) 20 \pm 6 months after LTx. Osteoporosis was present in 67% of the patients. Vertebral fractures were seen in 33% [15].

Segal and his associates tried to evaluate BMD, bone turnover, and calcium-regulating hormones in 29 patients (17 men, 12 women) from 2-12 years following LTx for non-alcoholic liver diseases and found bone mass changes in 65.5% of cases [16]. Baccaro *et al.* reported that approximately 21% showed osteoporosis and 35%, a low bone mass in a prospective, cross-sectional study of 23 female outpatient transplant recipients [17].

In the current study of the association between old age at transplantation, we did not observe a significant correlation between ages at the time of LTx and decreased bone mass. Baccaro *et al.* observed a significant association of older patient age at the time of liver transplantation with a decreased bone mass [17]. In contrast, Ninkovic *et al.* and Guichelaar *et al.* found an inverse relationship of age to decreased bone mass [18, 19].

Table 1. Pre-liver transplantation (LTx) factors affecting bone disease (BD) occurrence after LTx

		BD (post-LTx)						P value
		Normal		Osteopenia		Osteoporosis		
		78	78%	14	14%	8	8%	
Age (M ±SD) (years)		52.4 ±7.8		51.2 ±7.8		49.5 ±7.4		0.556
Pre-LTx BMI (M ±SD) (kg/m ²)		27.7 ±4.5		26.6 ±2.9		24.1 ±4.7		0.072
Sex	Male	73	80.2%	11	12.1%	7	7.7%	0.183
	Female	5	55.6%	3	33.3%	1	11.1%	
Smoking	Smoker	9	75.0%	3	25%	0	0.0%	0.279
	Ex-smoker	15	88.2%	0	0.0%	2	11.8%	
	Non-smoker	54	70.1%	11	15.5%	6	8.4%	
Alcoholic	Yes	0	0	5	100.0%	0	0.0%	0.000
	No	78	82.1%	9	9.5%	8	8.4%	
AHT FH	Yes	23	76.7%	4	13.3%	3	10.0%	0.888
	No	55	78.6%	10	14.3%	5	7.1%	
DM FH	Yes	32	72.7%	9	20.5%	3	6.8%	0.252
	No	46	82.2%	5	8.9%	5	8.9%	
Obesity FH	Yes	26	86.7%	4	13.3%	0	0	0.047
	No	52	74.3%	10	14.3%	8	11.4%	
MELD score		18	100.0%	20	28.0%	22	24.0%	0.0
Child Score	A	6	100.0%	0	0	0	0	0.006
	B	40	87%	3	6.5%	3	6.5%	
	C	32	66.7%	11	22.9%	5	10.4%	
Etiology of cirrhosis	HCV	64	82.1%	9	11.5%	5	6.4%	0.0
	HBV	4	80.0%	0	0	1	20.0%	
	AIH	0	0	2	100.0%	0	0	
	PBC	0	0	0	0	2	100.0%	
	Cryptogenic	10	76.9%	3	23.1%	0	0	
HCC	Yes	29	85.3%	4	11.8%	1	2.9%	0.336
	No	49	74.2%	10	15.2%	7	10.6%	

AHT – arterial hypertension, DM – diabetes mellitus, FH – family history, HCC – hepatocellular carcinoma, HCV – hepatitis C virus, HBV – hepatitis B virus, LTx – liver transplantation, BMI – body mass index

In a metanalytic study, HCV was postulated to augment C-terminal cross-linking telopeptide of type I collagen (CTX), with subsequent boosted bone resorption endeavors [20]. However, the direct pathogenic effect of HCV virus infection on bone is still questionable.

As HCV is the main cause of liver transplantation in Egypt, and as an Islamic country, alcohol is not a main cause. However, this fact does not exclude presence of a few cases with alcohol-related liver cirrhosis.

Being alcoholic was a risk factor for an increased prevalence of decreased bone mass after LTx in the present study, which is consistent with Meys *et al.* [21]. Reduced serum testosterone levels occurring in both

actively drinking alcoholics and patients with cirrhosis probably contribute to osteoporosis [21]. Low vitamin D levels have also been reported in about one-third of alcoholics with a low BMD, and vitamin D supplementation has been shown in one study to improve BMD at the wrist in some patients [22]. But, again the limited number of alcoholics included constrained thorough analysis of this point, added to the scarcity in the literature.

In the current study, a positive correlation was found between both excessive post-LTx weight gain and a family history of obesity with decreased bone mass. There are lots of speculations about adipose tissue production of adipokines, such as leptin, resistin, and adiponectin,

Table 2. Post-liver transplantation (LTx) factors affecting bone disease (BD) occurrence after LTx

Parameter		Post-LTx BD						P value
		Normal		Osteopenia		Osteoporosis		
		78	78%	14	14%	8	8%	
AHT post-LTx	Yes	34	73.9%	7	15.2%	5	10.9%	0.563
	No	44	81.5%	7	13.0%	3	5.5%	
DM post LTx	Yes	44	71.0%	12	19.4%	6	9.6%	0.028
	No	34	89.4%	2	5.3%	2	5.3%	
Post-LTx BMI (M ±SD) (kg/m ²)		26.9 ±3.7		22.8 ±1.5		28 ±3.5		0.004

AHT – arterial hypertension, DM – diabetes mellitus, LTx – liver transplantation, BD – bone disease, BMI – body mass index

Table 3. Frequency of post-liver transplantation (LTx) bone mineral density (BMD) according to the immunosuppressive drugs

Parameter		BD (post-LTx)						P value
		Normal		Osteopenia		Osteoporosis		
		78	78%	14	14%	8	8%	
Tacrolimus	Yes	50	74.6%	11	16.4%	6	9%	0.503
	No	28	84.8%	3	9.1%	2	6.1%	
Cyclosporine	Yes	28	84.8%	3	9.1%	2	6.1%	0.503
	No	50	74.6%	11	16.4%	6	9%	
MMF	Yes	63	78.8%	10	12.5%	7	8.7%	0.621
	No	15	75.0%	4	20.0%	1	5.0%	
Sirolimus	Yes	4	80.0%	0	0	1	20.0%	0.430
	No	74	77.9%	14	14.7%	7	7.4%	
Everolimus	Yes	5	71.4%	1	14.3%	1	14.3%	0.813
	No	73	78.5%	13	14.0%	7	7.5%	
Basiliximab	Yes	20	95.2%	0	0	1	4.8%	0.019
	No	58	73.4%	14	17.7%	7	8.9%	
Pulse steroid therapy	Yes	15	46.9%	10	31.2%	7	21.9%	0.000
	No	63	92.6%	4	5.9%	1	1.5%	

MMF – mycophenolate mofetil

Table 4. Binary logistic regression of predictors of bone disease occurrence after liver transplantation (LTx)

Parameter	P value	OR	95% CI	
			Lower	Upper
Age	0.927	0.996	0.906	1.094
Gender	0.593	0.565	0.07	4.589
BMI before transplantation	0.447	0.625	0.186	2.099
Family history of obesity	0.703	1.467	0.204	10.540
Etiology	0.024	0.289	0.098	0.851
Child score	0.006	0.179	0.053	0.606
Pulse steroids one year after LTx	0.251	0.294	0.036	2.381
DM 1 year after transplantation	0.003	12.476	2.294	67.859

AHT – arterial hypertension, DM – diabetes mellitus, LTx – liver transplantation, BMI – body mass index

which may negatively modulate BMD [23]. There is a scarcity of studies elucidating more clearly the role of previous variables in bone mass changes after LTx.

Development of diabetes after transplant also was reported as a risk factor in our study. Interestingly, there was evidence of interplay between diabetes and the potential mechanisms responsible for osteoporosis. Diabetes is often associated with changes in bone health, and the term “diabetic osteopathy” needs to be more precisely defined. Pathogenesis is related to insulin and subsequently IGF-1 deficiency (both have anabolic effects on the bone) [23].

In the current work, in agreement with Meys *et al.* and Diaz-Guerra *et al.*, cholestatic disorders were associated with a greater prevalence of osteoporosis, although limited numbers (2 recipients) were due to malabsorption of calcium and vitamin D, in addition to the interference of bilirubin levels in osteoblast function [21, 24]. The study of Baccaro *et al.* questioned this as a cause-and-effect relationship [17].

In this study, the severity of liver disease as measured by the CTP score at the time of LTx was ultimately related to decreased bone mass. Reduced bone formation in chronic liver disease has been linked to low levels of IGF-1 in serum [25]. In osteopenic rats, treatment with IGF-1 results in increased BMD. However, a direct causal link between IGF-1 levels and osteoporosis in chronic liver disease in humans has not yet been established [26].

A confirmed deleterious effect of GCs on bone mass was proved in the current study, as with Morris *et al.* and Diaz-Guerra *et al.* [24-27]. In contrast were the studies conducted by Segal *et al.* [16], Guichelaar *et al.* [19], and Baccaro *et al.* [17], who claimed that the use of corticosteroids as an immunosuppressive drug did not affect the bone mass.

The pathophysiology of GC induced bone disorder is multifactorial. Bone formation is inhibited by decreased proliferation, function (by reducing levels of type I collagen, IGF-1, and osteocalcin), and lifespan (by induction of osteoblast apoptosis). GCs also promotes osteoclastogenesis by increasing levels of the receptor activator of the nuclear factor- κ B ligand (RANKL) system. Other indirect effects of GCs also play a role in the mechanisms of bone loss (e.g. decreased intestinal calcium absorption, renal calcium wasting, and impaired gonadal hormone production). Furthermore, GCs may induce muscle weakness, which additionally delays post-transplant mobilization, with subsequent aggravation of bone loss [28].

The binary logistic regression has added substantial credibility to the post-LTx occurrence of DM, severity of liver disease, and HCV as independent predictors of

MBD occurrence one year after LTx. These results had not been verified previously in similar studies.

Collectively, this study reported a significant association between the severity of liver disease as measured by the CTP score at the time of LTx, HCV, and post-LTx DM and decreased bone mass. However, the deleterious effects of GCs and basiliximab on bone mass that were suggested by univariate analysis were refuted by binary logistic regression. Compared with previous studies, this report had the advantage of the prospective design along with the fairly large sample, as well as dealing with the usually overlooked Middle East population. However, missed pre-LTx baseline bony evaluations constituted a flaw in the current study which might be an alarm mandating more concern in Egyptian adopted protocols. Further multicenter national studies are still needed to elucidate the potential contributing factors for post-LTx metabolic bone diseases over longer follow-up periods.

Conclusions

Metabolic bone disease is suggested to be one of the most overlooked consequences after LTx which might poorly affect a patient's quality of life. Lifestyle modifications along with proper nutritional interventions are mandatory. DEXA scanning is recommended to be done yearly after LTx. Control of other metabolic complications after LTx might be worthwhile.

Ethics approval and consent to participate

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of the National Liver Institute (NLI IRB 00003413), Menoufia University. Written informed consent was obtained from both donors and recipients regarding surgery and research.

All included patients have approved publication.

Data used to support the findings of this study are included within the article.

Acknowledgements

All respect and indebtedness to the great professor Dr Omkolsoum Alhaddad for her unlimited, sincere, and priceless inputs allowing this work to be fulfilled.

Disclosure

The authors declare no conflict of interest.

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