Evaluation of Bone Mineral Metabolism After Liver Transplantation by Bone Mineral Densitometry and Biochemical Markers

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ABSTRACT

Aim. This study aimed to evaluate the course of bone and mineral metabolism after liver transplantation (LT) in patients with chronic liver disease.

Methods. One hundred four patients who had undergone LT and had a minimum of 6 months of follow-up after LT were included in this prospective cohort study. The following parameters were evaluated for each patient: preoperative and postoperative (postoperative day [POD]30, POD90, POD180) osteocalcin, bone-specific alkaline phosphatase (BALP), type 1 collagen, beta-C-terminal end telopeptide (β-CTx), vitamin D, parathyroid hormone (PTH), ALP, calcium, phosphate, sedimentation, and bone mineral densitometer scores (L2, L4, L total, and F total). The parameters were compared in terms of sex, presence of liver tumor (hepatocellular carcinoma [HCC; n = 19] vs non-HCC [n = 85]), and presence of autoimmune liver disease (autoimmune liver disease [ALD; n = 8] vs non-ALD [n = 96]).

Results. The median age of the patients (n = 81 men and n = 23 women) was 52 years (95% CI, 50-56). There was a significant change in the defined time intervals in parameters such as osteocalcin ($P < .001$), BALP ($P < .001$), β-CTx ($P < .001$), vitamin D ($P < .001$), PTH ($P < .001$), ALP ($P = .001$), calcium ($P < .001$), phosphate ($P = .001$), L2 ($P = .038$), L total ($P = .026$), and F total ($P < .001$) scores. There was a significant difference in POD90 ALP ($P = .033$), POD180 calcium ($P = .011$), POD180 phosphate ($P = .011$), preoperative sedimentation ($P = .032$), and POD180 F total ($P = .013$) scores between both sexes. There was a significant difference in POD180 osteocalcin ($P = .023$), POD180 β-CTx ($P = .017$), and preOP calcium ($P = .003$) among the HCC and non-HCC groups. Furthermore, we found significant differences in preoperative ALP ($P = .008$), preoperative sedimentation ($P = .019$), POD90 ($P = .037$) and POD180 L2 ($P = .005$) scores, preoperative ($P = .049$) and POD180 L4 ($P = .017$), and POD180 L total ($P = .010$) and F total ($P = .022$) scores between the patients with and without ALD.

Conclusion. This study shows that the bone and mineral metabolism of the LT recipients was negatively affected after LT. In addition, we showed that bone and mineral metabolism was more prominent in patients with HCC, and bone mineral density scores were higher in patients with ALD.

LIVER transplantation (LT) for patients with chronic liver disease (CLD) and hepatic malignancy has improved longevity and quality of life [1]. With the increased longevity among these patients comes the risk of some chronic diseases,

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such as post-transplant osteoporosis, which can potentially be a source of morbidity and mortality [2]. There has been a substantial reduction in bone density, especially within the first year of LT. The incidence of bone fractures among LT recipients was reported to be around 3.5%. The vertebral spine was the most common fracture site [3].

One of the main characteristics of osteoporosis is an alteration in bone quality and mineralization, which predisposes patients to the risk of bone injury or fracture [4]. The alteration in bone quality and mineralization passes through 4 phases. The first phase occurs before LT, which involves bone and mineral metabolism abnormalities in patients with liver failure. The second phase occurs after LT because of exposure to high-dose immunosuppressives. The third phase occurs after a few years, and it is because of the re-establishment of the bone. The last phase is characterized by the return of bone metabolic derangements associated with reduced graft function [5−7].

Multiple risk factors for osteoporosis after LT have been identified. Some of these risk factors are present before LT and are not specific to the underlying pathology. Such factors include female sex, diabetes mellitus, malnutrition, a sedentary lifestyle, smoking, excessive alcohol consumption, vitamin D deficiency, pretransplant hypogonadism, and preexisting bone mineral abnormalities [8,9].

Patients with CLD are reported as having osteoblastic dysfunction precipitated by many factors. One of the factors includes unconjugated hyperbilirubinemia, which has inhibitory effects on osteoblast proliferation and differentiation. They also have reduced mineralization and decreased synthesis of the collagen matrix. Studies have shown that patients with CLD have decreased availability of insulin-like growth factors, which potentiates a decrease in bone mass and density [8,9].

Post-transplant factors causing osteoporosis, osteopenia, and fractures among LT recipients include the choice of immunosuppressive therapy. Glucocorticoid therapy is associated with the apoptosis of osteoblasts and osteocytes. This will reduce bone formation, increase bone destruction, and decrease bone density [8−10]. The primary aim of the present study was to evaluate the course of bone and mineral metabolism (BMM) of CLD patients who have undergone LT. The secondary aim is to evaluate the relationship between the changes in BMM and various variables such as the sex of the patients, hepatocellular carcinoma (HCC), and autoimmune liver disease (ALD).

MATERIALS AND METHODS

Study Design

This prospective cohort study was conducted between September 2018 and July 2019 and included CLD patients who have undergone LT. We included 110 patients older than 18 years old who consented to be included in the study. All patients received the standard LT procedure at our institute. Patients who did not have a minimum of 180-day follow-up after LT and patients who received drugs affecting BMM (ie, calcium and vitamin D) were excluded from the study. Biochemical analyses from serum samples and bone mineral density (BMD) measurements were performed preoperatively and on postoperative days (POD) 30, 90, and 180. The serum samples were stored at −80°C until the analyses.

The results of the study were presented using several strategies. Initially, we performed a general analysis of all the parameters. Also, we analyzed the data according to sex, presence of HCC (HCC vs no-HCC), and presence of ALD (ALD vs non-ALD). Autoimmune hepatitis, primary biliary cholangitis, and primary biliary cirrhosis were included in the ALD group. The changes in BMM-related tests were initially analyzed according to the changes in the designated time intervals. Following these analyses, the changes in BMM according to the sex of patients with HCC and ALD were analyzed and presented separately. Finally, the factors associated with deviation from normal BMD were analyzed using logistic regression.

Definition and Classification of Patients According to BMD

Bone mineral density is mainly described as a T-score, which represents the number of SDs by which the BMD in an individual differs from the mean value expected in young, healthy people. Based on the World Health Organization report, BMD with a T-score above −1 SD is classified as normal BMD, a T-score between −1.0 and −2.5 SD is classified as osteopenia, and a T-score below −2.5 SD is defined as osteoporosis [11].

Sample Size and Power Analysis

The G Power 3.1 statistical package program (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany) was used for sample size calculation. The 1-sample t test was used to calculate the sample size for our study. The following parameters were used for the calculation: 2-tail, $\alpha = 0.01$, $\beta = 0.90$ (power= 90%), and effect of size = 0.4. It was concluded that the required minimum number of patients should be 97. However, 110 patients were included in the study to consider the loss of patients during the required follow-up period of 6 months.

Study Protocol, Ethics Committee Approval, and Financial Support

This study involving human participants was performed according to the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from Inonu University Institutional Review Board for Prospective Clinical Research (2018/49). The study was supported and funded by Inonu University Scientific Research Projects Coordination Unit (Project No: TSA-2018-1312).

Study Parameters

Sociodemographic features were as follows: age, sex (male, female), blood groups (0, A, B, AB), height (cm), weight (kg), body mass index (kg/m^2), smoking, alcohol use, antiviral drugs use, etiology (hepatitis B virus, hepatitis C virus, ALD, HCC, etc.), graft rejection, and immunosuppressive drugs.

Routine Biochemical Parameters

The following biochemical parameters were studied for this study: calcium (Ca), phosphate (P), alkaline phosphatase (ALP), erythrocyte sedimentation rate (ESR), parathormone (PTH), and 25(OH)D (Vitamin D) levels.

Biochemical Blood Parameters Indicating Osteoblastic and Osteoclastic Activity

We analyzed blood osteocalcin, bone-specific ALP (BALP), and C-terminal telopeptide of type 1 collagen (β-CTx) levels for this activity.

BMD Scan

The BMD scans were done using dual-energy X-ray absorptiometry (DEXA) and analyzed the following: lumbar (L2, L4, L total) and femoral (F total) BMD scores.

ELISA and Biochemical Analysis

Two tubes of blood were taken from the patients to determine the levels of 25(OH)D and PTH, ALP, calcium, and phosphorus. Samples for 25 (OH)D were protected from light, centrifuged, and analyzed immediately. In addition, 1 tube of blood was collected for enzyme-linked immunosorbent assay (ELISA) analyses. The blood samples were centrifuged at 4000 rpm for 7 minutes, and their serum was separated. The samples were placed in tubes and stored in a deep freezer at −80°C until analyzed. Osteocalcin (ng/ml), BALP (IU/L), and β-CTx (ng/L) were analyzed with the ELISA method using kits (Bioassay Technology Laboratory, Shanghai, China). We used an ELISA microplate reader (BioTek Synergy H1; BioTek Instruments, Winooski, Vt, United States) and a data analysis program (Gen5; BioTek Instruments). Serum levels of PTH (pg/mL), ALP (U/L), Ca (mg/dL), and P (mg/dL) were measured on an autoanalyzer (AU5832; Beckman Coulter, Brea, Calif, United States). ESR (mm) was determined by the classical Westergren method in the routine biochemistry laboratory. Serum Vitamin D levels (ng/mL) were analyzed by mass spectrometry on an API 4000 LC/MS/MS system (AB Sciex, Framingham, MA).

Statistical Analysis

The IBM SPSS Statistics 25.0 package program (IBM SPSS, Inc, Armonk, NY, United States) was used for the statistical analysis of this study. Qualitative variables were given as numbers and percentages. Quantitative variables were given as the median (lower and upper limits of the 95% CI for the median). The Shapiro-Wilk test was used to test the data for normal distributions. A nonparametric Freidman test was used for repeated measurements. The nonparametric Mann-Whitney U test was used to compare 2 independent groups. Patients were classified based on preoperative and POD180 BMD total vertebral body (L total) T-scores. Based on this definition (L total T-score), patients were compared as follows: patients with normal vs those with abnormal BMD and patients with osteoporosis vs those without osteoporosis. Then, the factors affecting the deviations in BMD were analyzed using logistic regression analysis. A value of $P < .05$ was accepted as statistically significant.

RESULTS

General Assessments

Data from 110 patients were collected for evaluation in the study. However, the 3- and 6-month data of 6 patients were missing and thus were excluded from the study. In total, 104 patients were evaluated for the present study. The median age of the patients was 52 years (95% CI, 50-56). Twenty-three (22.1%) patients were female, and 81 (77.9%) were male. Hepatocellular carcinoma was present in 19 patients (18.3%). Eight patients (7.7%) had autoimmune liver disease. The demographic and clinical characteristics of 104 patients are summarized in Table 1. The results of the ELISA and DEXA scans are summarized in Table 2. Osteocalcin ($P < .001$), BALP ($P < .001$), β-CTx ($P < .001$), vitamin D ($P < .001$), PTH ($P < .001$), ALP ($P = .001$), calcium ($P < .001$), and phosphate ($P = .001$) showed a statistically significant change in designated time intervals. The DEXA scan showed significant changes at designated time intervals in terms of L2 ($P = .038$), L total ($P = .026$), and F total ($P < .001$) scores. However, the L4 score ($P = .053$) showed changes over time, but it did not reach significance, although it was very close. The changes in ESR ($P = .668$) did not show any significant change over time.

Table 1. Demographic and Clinical Features of 104 Liver Transplant Patients

Variables	Results
Age [median (95% CI)]	52 (50-56)
Sex (n [%])	
Male	81 (77.9)
Female	23 (22.1)
HCC (n [%])	
Present	19 (18.3)
Absent	85 (81.7)
ALD (n [%])	
Present	8 (7.7)
Absent	96 (92.3)

ALD, autoimmune liver disease; HCC, hepatocellular carcinoma.

Comparison of Patients by Sex

Osteocalcin ($P < .001$), BALP ($P < .001$), and β-CTx ($P < .001$) levels showed significant changes in the pre-LT and post-transplant designated periods in the male patients. However, osteocalcin ($P = .080$), BALP ($P = .194$), and β-CTx ($P = .232$) levels did not show significant changes in the designated periods in female patients. In addition, the levels of osteocalcin, BALP, and β-CTx did not show significant changes among the 2 sexes in any designated period ($P > .05$).

Vitamin D ($P < .001$), PTH ($P = .002$), ALP ($P < .001$), calcium ($P < .001$), and phosphate ($P < .001$) levels showed significant changes in pre-LT and post-transplant periods in male patients. Only calcium levels significantly differed in female patients between the pre-LT and post-transplant designated periods. Between the 2 sexes, levels of ALP POD90 ($P = .033$), calcium POD180 ($P = .011$), phosphate POD180 ($P = .011$), and ESR preoperatively ($P = .032$) showed statistically significant changes.

In male patients, the DEXA scan results showed that the F total ($P < .001$) score showed significant changes between the pre-LT and post-transplant designated periods. However, L2 ($P = .189$), L4 ($P = .056$), and L total ($P = .129$) scores showed no significant changes in the designated periods, whereas, in the female patients, L2 ($P = .137$), L4 ($P = .401$), L total ($P = .132$), and F total ($P = .134$) showed no significant changes in the designated periods. Between the 2 sexes, only the F total score ($P = .013$) measured on POD180 was significantly different.

Table 2. Changes in Biochemical Blood Parameters and DEXA Measurements During the First Postoperative 6 Months

Variables [median	Results (95% CI)]	*P*
Osteocalcin (preoperative)	9 (8-10)	< .001
Osteocalcin (POD30)	15 (13-17)	
Osteocalcin (POD90)	17 (15-20)	
Osteocalcin (POD180)	14 (12-20)	
BALP (preoperative)	42 (37-48)	< .001
BALP (POD30)	51 (46-57)	
BALP (POD90)	57 (49-60)	
BALP (POD180)	45 (37-52)	
β-CTx (preoperative)	94 (81-124)	< .001
β-CTx (POD30)	233 (216-250)	
β-CTx (POD90)	142 (115-172)	
β-CTx (POD180)	166 (122-224)	
Vitamin D (preoperative)	5.7 (4.4-7.5)	< .001
Vitamin D (POD30)	5.9 (5.1-7.8)	
Vitamin D (POD90)	12 (9.1-15.5)	
Vitamin D (POD180)	16 (12.4-20.9)	
PTH (preoperative)	50 (41-70)	< .001
PTH (POD30)	42 (41-54)	
PTH (POD90)	53 (46-61)	
PTH (POD180)	65 (56-75)	
ALP (preoperative)	103 (93-111)	.001
ALP (POD30)	122(109-142)	
ALP (POD90)	111 (97-123)	
ALP (POD180)	115 (108-128)	
Ca (preoperative)	8.3 (8.2-8.6)	< .001
Ca (POD30)	9.1 (9.0-9.2)	
Ca (POD90)	9.2 (9.1-9.3)	
Ca (POD180)	9.1 (9.1-9.3)	
P (preoperative)	3.2 (3.0-3.3)	.001
P (POD30)	3.6 (3.4-3.8)	
P (POD90)	3.4 (3.2-3.7)	
P (POD180)	3.2 (3.2-3.4)	
ESR (preoperative)	16 (10-26)	.668
ESR POD30	11 (10-15)	
ESR (POD90)	14 (9-19)	
ESR (POD180)	14 (14-20)	
L2 (preoperative)	−1.3 (−1.5 to −0.9)	.038
L2 (POD30)	−1.3 (−1.6 to −1.0)	
L2 (POD90)	−1.3 (−1.7 to −1.1)	
L2 (POD180)	−1.3 −1.8 to 0.9)	
L4 (preoperative)	−1.6 (−1.8 to 1.3	.053
L4 (POD30)	−1.6 (−1.8 to −1.2)	
L4 (POD90)	−1.7 (−1.8 to −1.3)	
L4 (POD180)	−1.5 (−2.0 to −1.2)	
L Total (preoperative)	−1.3 (−1.5 to −1.1)	.026
L Total (POD30)	−1.2 (−1.5 to 0.8)	
L Total (POD90)	−1.3 (−1.6 to 1.1)	
L Total (POD180)	−1.4 (−1.6 to −1.1)	
F Total (preoperative)	0.1 (−0.1 to 0.4)	< .001
F Total (POD30)	−0.3 (−0.4 to 0.0)	
F Total (POD90)	−0.3 (−0.6 to 0.0)	
F Total (POD180)	−0.4 (−0.7 to −0.1)	

ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; β-CTx, beta-C-terminal end telopeptide; DEXA, dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; POD, postoperative day; PTH; parathyroid hormone.

Comparison of Patients With and Without HCC

In the HCC group, pretransplant and post-transplant levels of osteocalcin ($P < .001$), BALP ($P = .002$), and β-CTx ($P = .006$) showed significant changes. Similarly, in the non-HCC group, serum levels of osteocalcin ($P < .001$), BALP ($P < .001$), and β-CTx ($P < .001$) showed significant changes in the designated periods. Only osteocalcin POD180 ($P = .023$) and β-CTx POD180 ($P = .017$) levels showed significant changes among the patients with and without HCC.

In patients with HCC, only the pre- and post-transplantation levels of vitamin D ($P = .006$) and calcium ($P = .042$) were statistically different. Conversely, PTH ($P = .656$), ALP ($P = .145$), phosphate ($P = .408$), and ESR ($P = .695$) did not show significant changes. However, in the non-HCC group, vitamin D ($P < .001$), PTH ($P < .001$), ALP ($P = .001$), calcium ($P = .001$), and phosphate ($P = .002$) showed significant changes in the designated periods. Between the HCC and non-HCC groups, only calcium levels ($P = .003$) were significantly different, and other parameters showed no significant difference between the 2 groups.

The DEXA scans in the HCC group showed that F total score ($P = .011$) changed significantly over time. The L2 ($P = .168$), L4 ($P = .086$), and L total ($P = .232$) scores did not change significantly over time. In the non-HCC group, L4 ($P = .025$), L total ($P = .019$), and F total ($P < .001$) scores showed significant changes in the designated periods. There was a statistically significant difference between the 2 groups regarding the results of the DEXA scans. The results of the biochemical and specific serum markers and the DEXA scan of the different study groups are summarized in Table 3.

Comparison of Patients With and Without ALD

In the ALD group, the serum levels of osteocalcin ($P = .392$), BALP ($P = .241$), and β-CTx ($P = .266$) changed significantly over time. In the non-ALD group, the serum levels of osteocalcin ($P < .001$), BALP ($P < .001$), and β-CTx ($P < .001$) showed significant changes in the designated periods. The 2 groups did not show any significant difference in terms of osteocalcin, BALP, and β-CTx at any designated time point.

In the ALD group, phosphate ($P = .025$) and ESR ($P = .033$) showed significant changes over time. We could not find any significant change in the serum levels of vitamin D ($P = .615$), PTH ($P = .472$), ALP ($P = .478$), or calcium ($P = .508$) over time. However, in the non-ALD group, serum levels of vitamin D ($P < .001$), PTH ($P < .001$), ALP ($P = .001$), calcium ($P < .001$), and phosphate ($P = .002$) showed significant changes over time. Among the 2 groups, preoperative ALP ($P = .008$) and preoperative ESR ($P = .019$) showed significant differences.

The DEXA scan results showed that ALD and non-ALD had significant differences in F total scores over time (for ALD, $P = .01$; for non-ALD, $P < .001$). L2 POD90 ($P = .037$), L2 POD180 ($P = .005$), preoperative L4 ($P = .049$), L4 POD180 ($P = .017$), L total POD90 ($P = .042$), L total POD180

Table 3. Variation of Biochemical Blood Parameters and DEXA Measures by Some Independent Variables

Variables [median (95% CI)]	HCC (n = 19)	Non-HCC (n = 85)	*P* Value
Osteocalcin (POD180)	25 (15-33)	13 (11-18)	.023
β-CTx (POD180)	271 (209-360)	150 (111-207)	.017
Ca (preoperative)	8.8 (8.6-9.4)	8.2 (8.2-8.4)	.003
	ALD (n = 8)	Non-ALD (n = 96)	
ALP (preoperative)	228 (106-431)	99 (92-109)	.008
ESR (preoperative)	54 (25-110)	14 (9-25)	.019
L2 (POD90)	−2.3 (−2.6 to −1.6)	−1.2 (−1.5 to −1.0)	.037
L2 (POD180)	−3.0 (−4.0 to −2.7)	−1.2 (−1.5 to −0.7)	.005
L4 (preoperative)	−2.2 (−3.8 to −1.4)	−1.6 (−1.8 to −1.3)	.049
L4 (POD180)	−3.4 (−4.0 to −2.4)	−1.4 (−1.8 to −1.2)	.017
L total (POD90)	−2.1 (−3.0 to −1.8)	−1.3 (−1.6 to −1.1)	.042
L total (POD180)	−3.2 (−4.0 to −2.5)	−1.3 (−1.5 to −1.0)	.010
F total (POD180)	−1.5 (−2.1 to 1.1)	−0.3 (−0.5 to 0.0)	.022
	Male (n = 81)	Female (n = 24)	
ALP (POD90)	114 (101-132)	85.5 (67-123)	.033
Ca (POD180)	9.2 (9.1-9.3)	8.8 (8.7-9.1)	.011
P (POD180)	3.2 (3.2-3.4)	3.7 (3.4-4.0)	.011
ESR (preoperative)	12 (9-25)	27 (15-54)	.032
F total (POD180)	−0.3 (−0.5 to 0.1)	−1.1 (−1.5 to −0.5)	.013

ALD, autoimmune liver disease; β-CTx, beta-C-terminal end telopeptide; ESR, erythrocyte sedimentation rate; DEXA, dual-energy X-ray absorptiometry; HCC, hepatocellular carcinoma; POD, postoperative day.

(*P* = .010), and F total POD180 (*P* = .022) showed significant differences between the ALD and non-ALD groups. All the data regarding the analyses of the parameters are summarized in Table 3.

Multivariate Logistic Regression Analysis

The patients were examined based on L total T-score in the preoperative and POD180 periods, and the risk factors affecting the BMD changes in the mentioned period were analyzed.

<H3>Patients with normal vs abnormal BMD (preoperative T-score).

Age, sex, BMI, Child score, Model for End-Stage Liver Disease score, presence of HCC, presence of ALD, and blood tests (albumin, bilirubin, osteocalcin, BALP, β-CTx, vitamin D, PTH, ALP, calcium, phosphate, ESR) variables were included in the backward stepwise logistic regression model. It was found that the presence of ALD (odds ratio [OR] = 11.2; *P* = .01; 95% CI, 1.6-199) and blood phosphate level (OR = 2.3; *P* = .015; 95% CI, 1.18- 4.54) was associated with the deviation in preoperative BMD. However, the logistic regression analysis using the mentioned model determined that high preoperative ESR (OR = 1.01; *P* = .046; 95% CI = 1.007-1.03) was associated with preoperative osteoporosis.

<H3>Patients with normal vs abnormal BMD (POD180 T-score).

The mentioned variables were included in the backward stepwise logistic regression model. High BMI (OR = 0.89; P = .044; 95% CI, 0.79-0.99) was found to be associated with the deviation in POD180 BMD. Similarly, the logistic regression analysis using the mentioned model determined that ALD (OR = 28.9; *P* = .009; 95% CI, 2.36-356) was associated with POD180 osteoporosis.

DISCUSSION

Post-transplant osteoporosis is a major cause of morbidity among LT recipients [2,6,9]. It is a systemic disease that manifests as reduced bone mass and architectural distortion of the bone, resulting in increased bone fragility and susceptibility to fractures. The incidence of post-transplant osteoporosis is up to 48% within 1 year of LT [2,3]. Recognized risk factors for osteoporosis among recipients of LT include cholestatic hepatic diseases, hypogonadism, alcoholism, and abnormalities in vitamin D metabolism. Other risk factors include high-dose steroids, other immunosuppressive medications such as tacrolimus and cyclosporine, immobility, and lack of adequate nutrition [8−10]. The architectural changes in the bone predispose these patients to atraumatic fractures or fractures after minimal trauma [3]. Abate et al [12] reported the fracture incidence to be 14.6% within 1 year of LT. The most common sites affected by post-transplant fractures were the spine, ribs, wrist, hip, and pelvis [3,12].

The main cells responsible for bone homeostasis are osteoblasts and osteoclasts. The functions of these cells vary. Although the resorption of bone is done by osteoclasts, the formation of new bone is done by osteoblasts [13−15]. The balance between bone formation and resorption is maintained tightly, and any abnormality may result in bone diseases such as osteoporosis. To maintain this balance, the 2 cells are believed to be in constant communication with each other through direct cell-cell contact, extracellular matrix interaction, and cytokines [15]. Osteoclasts' formation, differentiation, and apoptosis are affected by osteoblast through pathways, such as osteoprotegerin pathway (OPG), receptor activator of NF-kB ligand (RANKL) pathway, Receptor activator of NF-kB pathway (RANK), first apoptosis signal pathway (Fas) and first

apoptosis signal ligand pathway (FasL). In the same way, osteoblast formation and function is also affected by osteoclast. The cytokines released from the resorbed bone matrix, such as transforming growth factor-β and insulin-like growth factor-1, also affect the activity of osteoblasts [16−18].

The state of bone metabolism and the functions of osteoblasts and osteoclasts can be estimated by measurement of serum markers such as β-CTx, BALP, osteocalcin, calcium, and phosphate. Some of these are markers of bone formation; others are markers of bone resorption and osteoclast genesis [19−22].

Bone formation can be assessed by serum measurement of the byproduct of active osteoblasts produced during their development or osteoblastic enzymes. Some of the markers are measured in serum or plasma. Some commonly used markers are BALP, osteocalcin, and the carboxy- and amino-terminal propeptides of type 1 collagen [19−22].

The assessment of bone resorption was initially cumbersome because the markers used were measured in the urine and required 24-hour urine collection. The urinary markers of bone resorption included pyridinoline and deoxypyridinoline [19−22]. Serum and plasma markers of bone resorption are now available. The commonly used ones include carboxy-terminal and amino-terminal cross-linked telopeptides of type 1 collagen. Between these 2 markers, the carboxy-terminal cross-linked telopeptide of type 1 collagen is preferable as the marker of choice. It is generated by cathepsin K activity. It contains an aspartyl-glycine motif that can undergo spontaneous isomerization and racemization-generating isoforms. One of the isoforms is the β-form (β-CTx), which is the isoform usually measured in the serum [19−22].

In our study, we found a significant change in the defined time intervals in parameters such as osteocalcin, BALP, β-CTx, vitamin D, PTH, ALP, calcium, phosphate, L2, L total, and F total scores.

CONCLUSIONS

This study showed that BMM was more prominent in patients with HCC, and BMD scores were higher in patients with ALD. In other words, this study showed that ALD was associated with deviations in BMD measured preoperatively and at POD180.

DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY

Data will be made available on request.

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