Pitfalls in the interpretation of bone turnover markers in liver transplantation

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Introduction

Osteoporosis is reported in 20-50% of patients with chronic liver disease awaiting orthotopic liver transplantation (OLT), and vertebral fractures are prevalent in 3.5-36%. It has proven difficult, however, to identify factors associated with increased fracture risk in these patients. The association between clinical parameters such as primary liver pathology or severity of liver disease, bone mineral density (BMD) and fracture risk is inconsistent and generally poor. The value of bone turnover markers (BMTs) in the prediction of bone loss and fracture risk is as yet to be established in liver transpplant recipients.

The aim of our study was to assess the value of BTMs in the prediction of bone loss and fracture risk within the first year after OLT.

Methods

Patients: Consecutive OLT recipients between 2008-2011, in whom data were available on the bone turnover markers P1NP, osteocalcin, BALP and CTX from initial measurements, or from measurements undertaken in Biobank stored sera at screening and at 3, 6 and 12 months post-OLT .

Inclusion criteria: Availability of BMD data and spinal radiographs at screening and 6 and 12 months post-OLT.

Exclusion criteria: treatment with bone-modifying agents or obtaining a second OLT or renal tranplantation during the study period

BMD-measurement: BMD was measured at the lumbar spine and femoral neck using dual energy X-ray absorptiometry (DXA- Hologic QDR 4500, Hologic inc. Waltham, MA, USA

Vertebral fracture assessment: Conventional spinal radiographs were assessed by two independent observers using Genant's semi-quantitative method

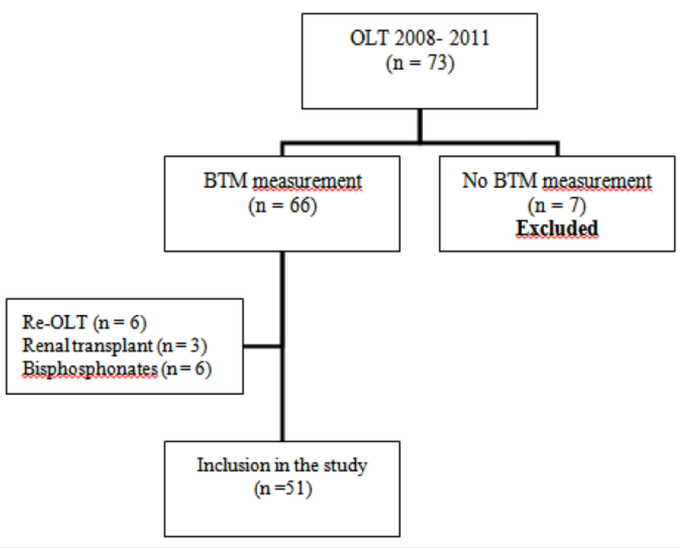

Figure 1: Study flow chart

Results

Demographic data

P1NP measurements and stored sera were available at screening in 66 patients (80% male) with a median age of 59 years (range 23-66yrs). Most common primary liver disease was alcoholic liver disease (41%) viral liver disease (26%) and cholestatic liver disease (4%).

Osteoporosis and osteopenia were respectively present in 16 and 33 % of patients at the lumbar spine (LS) and 4 and 44% at the femoral neck (FN).

Vertebral fractures were prevalent at time of screening in 34 patients (67%), mostly grade 1.

Bone turnover markers

Mean P1NP level was 82 ± 47 ng/mL (normal < 59 ng/mL). Mean osteocalcin levels was 9 ± 4 ug/L (mean Z-score -0.9 ± 1.6), mean BALP was 22 ± 9 U/L (mean Z-score 0.82 ±1.7) and mean CTX level was 397 ± 326 pg/mL (mean Z-score 2.16 ± 3.5). Changes in BTM after OLT shown in **Figure 2**.

Changes in BMD 12M after OLT

FN BMD decreased significantly after OLT ($p < 0.005$) remaining stable thereafter. There was no significant change in LS BMD after OLT.

Incident fractures 12M after OLT

New fractures were documented in 43% of patients within the first year after OLT.

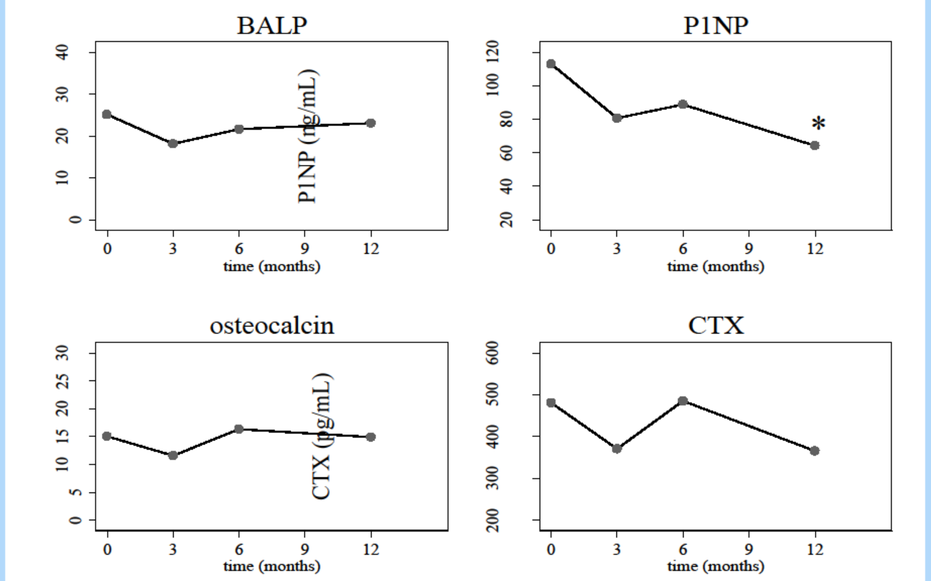

Figure 2: Changes in bone turnover markers after OLT; P1NP = pro-collagen type 1 amino-terminal pro-peptide; BALP= bone specific alkaline phosphatase; CTX = cross-linked C-terminal telopeptide of type I collagen; * = significant change compared to screening, p-value < 0.05

Predictive value of BTMs for changes in BMD or fracture risk

Higher CTX levels were associated with a decrease in LS ($p = 0.008$) as well as in FN BMD ($p=0.039$) and with an increase in fracture risk ($p = 0.033$).

An increase of BALP levels between screening and 6 months after OLT was associated with an increased risk of fractures ($p = 0.001$).

Other bone turnover markers measured in this study before, or during the first year after liver transplantation had otherwise no predictive value for bone loss or fracture risk in the first year after transplantation

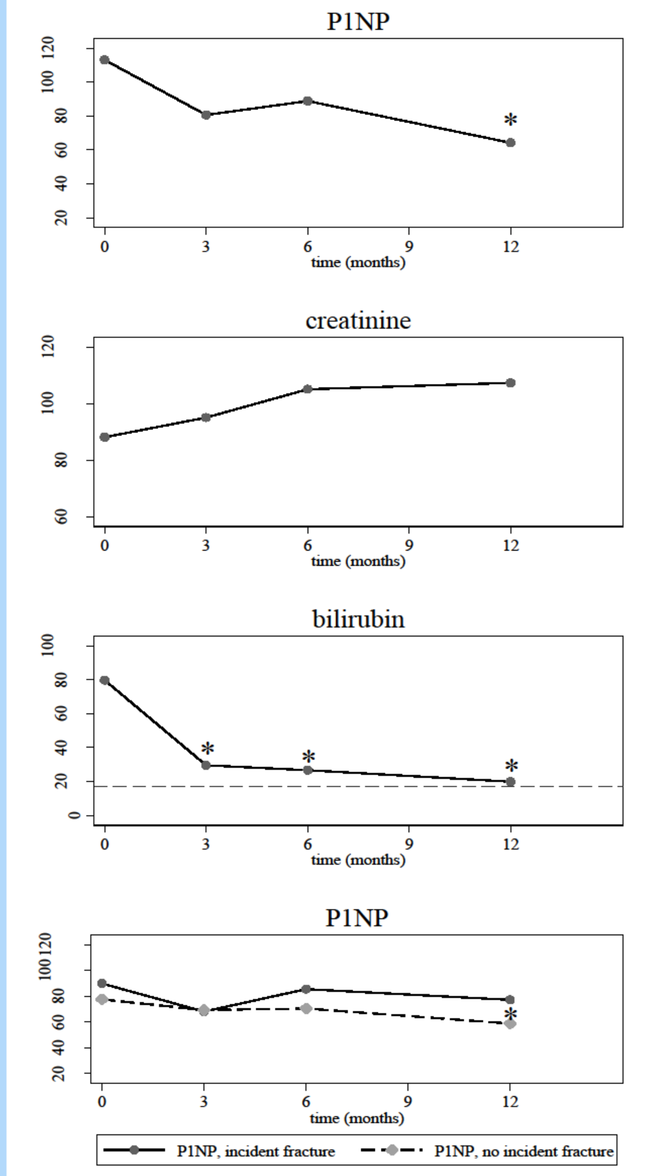

Figure 3: Factors potentially affecting the interpretation of bone turnover markers after liver transplantation; P1NP = pro-collagen type 1 amino-terminal pro-peptide. * = significant change compared to screening, p-value < 0.05.

Conclusion

- The presence of elevated CTX levels before OLT, and an increase in BALP after OLT reflect best the risk for bone loss and fracture after orthotopic liver transplantation
- However, chronic liver disease is associated with increased extra-skeletal collagen synthesis and degradation, resulting in pitfalls in the interpretation of collagen-derived bone turnover markers, so that caution is advocated with the use of these markers in therapeutic decision making in the management of skeletal complications of end-stage liver disease before and after orthotopic liver transplantation.

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