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Bone Disease After Organ Transplantation with Special Regard of Post Transplantation-Osteoporosis After Liver Transplantation

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1. Introduction

The frequency of disorders of bone metabolism (osteopenia, osteoporosis) after liver transplantation is stated up to 50%. The first three to six months after transplantation are linked to the greatest bone density loss. The probability for sustaining a fracture in the post-transplantation phase is indicated with up to 65%. Most fractures are sustained still within the first two years after the transplantation and the most common site is the spine followed by costal fractures and femoral neck fractures. Vertebral body fractures and femoral fractures in particular cause a dramatic limitation of the patients' mobility and quality of life; in addition, an increase of mortality occurs.

2. Definition of osteoporosis

Osteoporosis is a systematic skeletal disease; its course is characterized by a reduction of bone mass, a microarchitectural deterioration of bone and thus an increase of bone fragility and a susceptibility to fracture. The reference standard of the WHO allows quantifying the extent of bone mineral density reduction with DXA method. A T-score – the standard deviations of the measurement from the average of 30-year-old healthy Caucasians – between -1 and -2.5 indicates osteopenia whereas scores below -2.5 indicate osteoporosis. After occurrence of one or several fractures due to low-energy trauma an apparent osteoporosis is existent.

3. Pathophysiology

Genesis of post-transplantation bone disease after liver transplantation (LT) is multifactorial, it comprises among others the pre-existent bone density loss in case of chronic liver disease, hypogonadism, deficit of vitamin D and increase of parathyroid hormone, malnutrition, nicotine and alcohol abuse. These factors will be potentiated by postoperative immobility, the medical substitution of immunosuppressives, glucocorticoids and of heparins.

3.1 Hepatic osteodystrophia

Osteoporosis in combination with chronic liver diseases is based on the imbalance between bone formation and degradation. The existing cirrhosis is often a result of alcohol abuse. Bone biopsies from patients with ethyl toxic liver cirrhosis show a lower trabecular bone volume. At the same time, a clear reduction of osteoblast activity and a lower bone formation rate occur.

Patients with primary biliary cirrhosis (PBC) often show lower vitamin K levels. Vitamin K is linked to the synthesis of osteocalcin and has an anti-apoptotic effect on osteoblasts; lowered vitamin K levels thus can favour an osteopenia in case of PBC.

A hyperbilirubinemia is associated with proliferation-inhibiting effects on osteoblasts. However, a direct link to lower bone mineral density is not proven. Bone resorptive components play an important pathophysiologic role for the hepatic osteodystrophia. In the course of the inflammatory process and the fibrosis in the liver, there is an increase of IL-1, IL-6 and TNFα. These inflammatory mediators lead to a release of RANKL from osteoblasts. Due to the linking to RANK, which is expressed by osteoclasts, there is an increase in the genesis of osteoclasts from progenitor cells and in osteoclast activity. This leads to an acceleration of bone resorption. A hypogonadism often occurs in patients with chronic liver disease. The reasons are the reduction of releasing hormones of the hypothalamus and the reduction of gonad function. That leads in women to low levels of oestrogens which induce the activation of bone resorption and thus a bone density loss. In men that leads to lowered testosterone levels and elevated levels of oestrogens due to the increased aromatase reaction with augmented transformation of testosterone to oestrogen.

The growth factor IGF-1 is produced to a large extent by liver cells; the decreased liver function due to chronic liver disease thus causes lowered IGF-1 levels. Glucocorticoids are applied within the therapy of autoimmune hepatitis and immediately after liver transplantation; they influence the bone metabolism in many ways.

3.2 Immunosuppressive therapy

The immunosuppressive therapy is indicated as another important factor for the development of post transplantation bone disease after liver transplantation. Especially the effect of glucocorticoids on the bone metabolism must be pointed out. Particularly in the first six months after liver transplantation, high dosage glucocorticoids are used. Because an indirect link between the applied amount of cortisone and the bone mineral density after transplantation is assumed, cortisone has a quite important effect on the bone metabolism in liver transplanted patients.

The effects of corticosteroids on the bone metabolism after liver transplantation can be divided into two stages. In the first six months after the transplantation, glucocorticoids provoke a decoupling between bone formation and resorption due to a decrease of osteoblast activity and a simultaneous increase of osteoclast activity. This decoupling is marked by a rapid loss of bone mineral density and accumulated occurrence of fractures. In the ensuing period and thus the reduction of applied cortisone doses, the bone density loss is firstly slowed down and finally, due to the reoccurring of coupling of bone formation and resorption, it comes to the recovery of bone metabolism.

Steroids have many direct and indirect effects on the bone metabolism. Indirect effects do not concern single cell lines, their targets are in the field of endocrinologic processes which are linked to the bone metabolism.

Glucocorticoids conduct to a lowered expression of calcium channels in the intestine and thus to lowered calcium absorption and they increase the kidney's excretion of calcium. The consequence is a calcium loss which can lead to a secondary hyperparathyroidism and to a higher osteoclast activity.

Glucocorticoids influence the hypothalamo-hypophyseal axis. They induce an inhibition of growth hormone production and of testosterone or oestrogen production. The consequence is a higher osteoclast activity and a lower osteoblast activity.

In combination with the occurrence of a steroid myopathy, the limitation of musculoskeletal interaction due to glucocorticoids leads to a further decrease in osteoblast activity. The consequence is a higher osteoclast activity and a lower osteoblast activity.

A direct effect on bone resorption originates from changes in the RANK Ligand/osteoprotegerin system. Under treatment with glucocorticoids, an increased synthesis of RANK Ligand from osteoblasts can be observed, whereas osteoprotegerin synthesis is inhibited.

RANK Ligand binds to the RANK receptor on osteoclasts and thus increases the osteoclast activity. At the same time, the lowered expression of osteoprotegerin facilitates the docking of RANK Ligand on RANK because osteoprotegerin is unable to neutralize RANK Ligand.

M-CSF is essential for osteoclast maturation and its production is increased by the glucocorticoids. The inhibition of caspase 3 leads to a decreased apoptosis rate of osteoclasts and results in longer survival time of osteoclasts. Moreover, glucocorticoids cause a higher production of collagenase 3 so that the synthesis of type I collagen is inhibited. The result of liver transplantation is an elevated resorption of bone matrix.

The effects that have glucocorticoids on osteoblasts are closely linked to the increased expression of caspase 3 and the formation of the dickkopf-related protein. Caspase 3 causes an increase of the osteoblast apoptosis rate whereas the dickkopf-related protein inhibits the genesis of osteoblasts. In course of a glucocorticoid therapy, the apoptosis of osteocytes is increased and due to a feedback mechanism, there is an increase of osteoblast activity. The glucocorticoids also influence the differentiation of mesenchymal stem cells. Due to stimulation of the PPARγ2, the mesenchymal stamm cells differenciate increasingly to adipozytes instead of osteoblasts.

In addition, in course of a glucocorticoid therapy less Runx2 is generated and in consequence, the osteoblast genesis is increased additionally.

Apart from steroids, other immunosuppressive drugs are applied in course of liver transplantation. Cyclosporin A, tacrolimus and azathioprine are applied as traditional immunosuppressive drugs; but also more recent substances as sirolimus and mycophenolate mofetil (MMF) are applied more and more frequently at present.

Cyclosporin A, tacrolimus and mycophenolate mofetil have very different effects on the bone metabolism. Osteopenia occurred more often by appliance of cyclosporine than by tacrolimus (whereas mycophenolate mofetil seems not to have negative effects on the bone mineral density).

The bone status before transplantation functions as predictive factor for the bone density loss after liver transplantation. Low bone density data before transplantation thus increase the risk to suffer after the liver transplantation from bone density loss. The extended immobilisation in course of the hospitalization and an inadequate low-calcium diet are still linked to post-transplantation bone disease.

3.3 Vitamin D and parathyroid hormone deficiency

Patients suffering from chronic liver disease often present after liver transplantation a lowered vitamin D status and increased parathyroid hormone levels. The parathyroid hormone level seems to correlate negatively with the patients' bone mineral density.

Disorders of bone metabolism already develop during the progression of chronic liver disease and are closely linked with its pathogenesis. Analysis of the lowered bone density prevalence are available for cholestatic liver diseases, for viral hepatitis, for alcohol-related liver diseases and for hereditary haemochromatosis.

By interpretation of bone density loss, it has to be considered that obesity and ascites may lead to measurement errors. It is thus indispensable to consider other risk factors (hypogonadism, immobility, low body mass index) to evaluate the risk of fracture.

Because the extent of the bone metabolism disorder at the time of liver transplantation has an important effect on the further progression, an evaluation of bone turnover and skeletal status prior to transplantation is needed. Among bone mineral density measurement, spinal radiographs are used to detect vertebral body deformations. Blood tests include calcium and phosphate levels, alkaline phosphatase, parathyroid hormone levels and 25-hydroxycholecalciferol as indicator of vitamin D status.

4. Therapy

To date, no evidence-based recommendations exist for the prophylaxis and therapy of bone metabolism disorders by chronic liver diseases and after liver transplantation. The need for compensation of the deficiency in 25-hydroxycholecalciferol, for a daily calcium supply of 1-2 gram and for a reduction in glucocorticoid dosage with the aim of a glucocorticoid-free immunosuppression is consensus.

To avoid bone mass loss, several antiresorptive agents are applied. But most of these studies demonstrate considerable deficiencies and do not comply with the requirements of evidence-based medicine.

The database to the application of biophosphonates after liver transplantation is limited. It refers to the application of pamidronate, zoledronate, ibandronate intravenously and etidronate and alendronate per os.

A therapy with calcitonin (40 IU/d by 17 patients) started after liver transplantation showed, compared to etidronate (400 mg p.o. for 15 days every 3 months, 23 patients), a significant increase in bone mineral density after one year of 6.4 vs. 8.2%. The examined bone formation markers osteocalcin and procollagen I propetid have been unaltered high in both groups during time of treatment. Because of the absence of a control group a conclusion about the efficiency is not possible.

Against that, Hay has been unable to prove in a controlled 12 months study effects on bone mineral density and fracture incidence in patients with primary sclerosing cholangitis (n=37) and with primary biliary cirrhosis (n=26) by application of calcitonin (100 IU daily for 6 months after transplantation).

In a survey with 53 patients was observed that application of alfacalcidol in combination with calcium and cyclic etidronate after liver transplantation does not influence bone density loss and fracture incidence. Against that, Neuhaus has proven an increase in bone mineral density on lumbar spine for all treatment groups by a therapy started six months after liver transplantation with calcitriol with or without calcium and sodium fluoride.

4.1 Alendronate

The effect of alendronate in comparison with etidronate has been examined in 2003 in 32 women with PBC. 16 patients each received either 10 mg alendronate/day or etidronate 400 mg/day for 14 days every 3 months. 26 patients have completed the two-year study. There were no changes in lumbar and femoral BMD in the etidronate group. After 2 years, lumbar spine BMD increased by 5.8±1.4% in patients on alendronate vs.1.9±1.1% in patients on etidronate; femoral neck BMD increased by 3.5±0.9% vs. 0.4±1.3%. No new vertebral fractures occurred.

A prospective uncontrolled study examined in 136 patients awaiting liver transplantation the effect of a prophylactic alendronate therapy in case of densitometric detection of osteoporosis and osteopenia and in patients whose initial normal BMD decreases after liver transplantation. It was possible to prove not only the prohibition of bone density loss post transplantationem in patients with initial osteoporosis diagnosis but an increase of bone mineral density after two years.

This result is consistent with the one for a therapy with alendronate, calcium and calcitriol by 59 patients post liver transplantation who had in comparison with an historic control group without an antiosteoporotic therapy a significant increase in mineral density after 12 months and no fractures [22].

In a prospective, controlled, open study with 98 patients with liver cirrhosis for over 24 months, the same authors have shown a significant increase in mineral bone density on lumbar spine, femoral neck and femur total by therapy with 70 mg alendronate weekly in the first three months after liver transplantation compared to a control group with patients receiving only calcium and calcitriol. Vertebral body fractures emerged in both treatment groups (18.8% by calcium and calcitriol and 6.8% by alendronate added). Osteocalcin and urinary DPD decreased in the alendronate group according to baseline values by -35.6% and -63% and increased in the control group by 30% and 15%.

4.2 Pamidronate

A not-randomised study reports on a reduction of fracture risk due to monthly infusion with pamidronate three months before and up to nine months after liver transplantation. However, only 13 patients have been treated with pamidronate, so a generalization is out of question.

In a prospective examination with 99 patients, it was not possible to prove after a singular infusion of pamidronate pre-liver transplantation any effects on the development of bone mineral density and the fracture rate in the first year post liver transplantation.

A histomorphometric examination describes the bone remodeling at tissue level in paired biopsies before and three months after successful liver transplantation in seven patients after a single infusion of pamidronate before liver transplantation in comparison to five untreated patients. In contrast to the untreated patients, those with pamindronate treatment did not show an increased bone formation rate but a significant reduction in the size of resorption lacunae. The data suggest a reduction of postoperative high turnover due to preoperative pamidronate therapy.

Recently, the results of a randomised, double-blind, placebo-controlled study with 79 patients have shown that the application of 90 mg pamidronate (38 pat.) two weeks before and three months after liver transplantation leads to a significant increase of lumbar BMD after 12 months with an increase in density of 2.9% vs.1%. There was no difference in the density loss of femoral neck and the fracture incidence.

4.3 Zoledronate

The ability to prevent bone loss after infusion of zoledronate within 7 days of transplantation and 1, 3, 6 and 9 months after liver transplantation in 32 patients compared to 30 placebo-treated ones could be demonstrated.

Moreover, in a controlled, prospective, open study after eight infusions each of 4 mg zoledronate in the first 12 months after liver transplantation in 47 patients has shown a reduction in serological and histological bone turnover markers and a reduction of fracture incidence.

4.4 Ibandronate

In an open, prospective, placebo-controlled study, 34 patients have been treated for over one year with 2 mg ibandronate every 12 weeks intravenously, calcium and cholecalciferol starting on the day of liver transplantation. The control group received exclusively calcium and cholecalciferol. BMD measurements were carried out after 3, 6, 12 and 24 months. Fractures have been detected constantly.

A further reduction of BMD at all measured sites in the first few months after liver transplantation has been shown for all patients. However, after 12 and 24 months ibandronate treated patients demonstrated significant higher BMD and lower prevalence of fractures.

5. Conclusion

In summarising, a great variability can be observed in the available data about the extent of the impact on BMD and on the risk of fracture due to application of bisphosphonates or other osteotropic agents in course of a liver transplantation. The capability to reduce the BMD loss in the early stages after liver transplantation due to bisphosphonates is reported consistently. Despite this ambiguity, it has to be recommended to evaluate the bone status

before liver transplantation and to start a bisphosphonate therapy in case of osteoporosis. For differential therapeutic outcomes, randomised, double-blind, prospective and controlled studies are necessary. Informing and guiding patients to a bone-healthier lifestyle and the elimination of avoidable risk factors remains unaffected.

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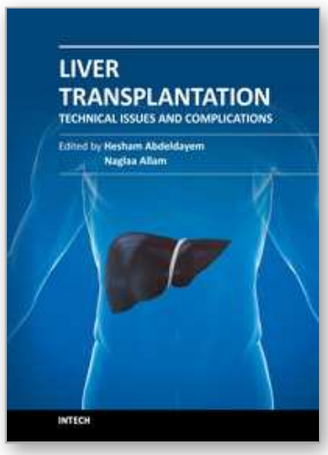
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This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoprolifrative disorders (PTLD), have been covered in more than one chapter.

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