Aseptic necrosis of bone following a successful kidney transplantation
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The intention of this study was to try to make a contribution to the etiology of aseptic necrosis of bone following a successful kidney transplantation.

In the Introduction an outline is given of the present study after some general remarks with regard to aseptic necrosis have been made. It is emphasized that the incidence of aseptic necrosis in transplanted patients is much higher than in patients treated with corticosteroids for other reasons. It is mentioned that the extent of renal osteodystrophy before transplantation and the amount of corticosteroids administered thereafter are most likely the two important factors for developing aseptic necrosis after transplantation.

In the first part of the study a review of the literature is given. Chapter 1 contains the role of corticosteroid therapy in the development of aseptic necrosis. From the reports of the literature two pathogenic mechanism emerge: the fat embolization theory and the osteoporotic theory in the presence of renal osteodystrophy. In our opinion, there is more evidence for the osteoporotic theory. Considering the administered doses of corticosteroids, it can be said that the reported data lend little support to the hypothesis that the risk of developing aseptic necrosis is higher when an increased dose of corticosteroids has been prescribed. Additionally, there appeared to be a wide variation in the corticosteroid-dosages per center as well between the centers.

In Chapter 2 the effects of corticosteroids on bone are discussed on the basis of the data in the literature. There is apparently a great resemblance between what is happening with bone in patients on corticosteroid therapy and in patients with renal failure.

In the first part of Chapter 3 the pathophysiology of renal osteodystrophy is described. It is stated that the main factor responsible for development of renal osteodystrophy in patients with early renal failure is a defect in the Vitamin D metabolism. In patients with advanced renal failure other factors are also important. In patients on dialysis renal osteodystrophy, especially osteomalacia, is progressive when the time spent on regular hemodialysis becomes longer. The second part of Chapter 3 contains a discussion about the diagnostic aspects of renal osteodystrophy. It is emphasized that under certain conditions serum calcium values in patients on dialysis can reflect the extent of osteomalacia.

For several reasons parathyroid hormone levels are not useful as parameter for assessing the extent of renal osteodystrophy, especially in dialysed patients.

In Chapter 4 the literature on the natural history of renal osteodystrophy after transplantation is reviewed followed by a review of its influence on the development of aseptic necrosis. Renal osteodystrophy resolves slowly (until 4 years) after a successful kidney transplantation. The data on the influence of renal osteodystrophy on the development of aseptic necrosis are controversial. Hypophosphatemia is a common finding at
transplantation; in cases of long standing hypophosphatemia the risk of developing aseptic necrosis seems to be higher.

In Chapter 5 the role of parathyroid hormone in the development of aseptic necrosis discussed. After transplantation the parathyroid hormone levels become normal in some patients and remain high in others. There seems to be no correlation between the parathyroid hormone levels and the development of aseptic necrosis after a successful renal transplantation.

In the second part of this thesis our own work is described and the results are discussed.

In Chapter 6 the selection criteria for participation of the patients in this study are given, followed by the plan of investigation and the methods used.

The results are shown in Chapter 7. At 2 and 3 months after transplantation the patients with aseptic necrosis had received significantly more corticosteroids than the patients without aseptic necrosis. However, responsible for this difference were only the doses of corticosteroids administered at 1 month after transplantation to the patients of group I (0-6 months on dialysis). The patients with aseptic necrosis of group 4 (> 24 months on dialysis) received lower corticosteroid doses in the first 3 months after transplantation compared with the patients without aseptic necrosis. In general, the doses of corticosteroids given after transplantation were lower in those patients who were treated longer with regular hemodialysis.

The mean serum calcium value during the last year on dialysis before transplantation was significantly lower in the patients with aseptic necrosis. However, this difference was only demonstrable between the patients with and without aseptic necrosis of group 3 (7-12 months and 13-24 months on dialysis). After transplantation the serum calcium values were similar in both categories of patients.

The serum phosphate values before transplantation showed no difference between patients with and without aseptic necrosis. In contrast, after transplantation those values were significantly lower for a longer period of time in the patients who developed aseptic necrosis.

The combination of a low mean serum calcium value in the last year before transplantation and a low serum phosphate until at least 6 months afterwards presents a high risk for developing aseptic necrosis.

Those patients, who were on dialysis for a short period of time, developed aseptic necrosis after transplantation almost only if they had received large doses of corticosteroids within the first month. When the time spent on dialysis became longer the mean serum calcium value in the last year before transplantation is the more determinant factor with regard to the development of aseptic necrosis afterwards.

The parathyroid hormone level remained high for a long period of time in some of the patients. No relation was found between those levels and the development of aseptic necrosis. However, a strong correlation could be found between the time of treatment
with hemodialysis and the parathyroid hormone level after transplantation; the levels remained high in patients treated for more than 1 year.

Chapter 8 the results are discussed and conclusions are drawn. The incidence of aseptic necrosis reported in the literature, varies widely because the selection of the patients varies. With regard to some general aspects such as age, sex and time on regular dialysis, our patients do not differ from the patients reported in the literature.

The controversial data in the literature concerning the influence of the corticosteroid dosage on the development of aseptic necrosis could be explained by the relationship found between the time of regular hemodialysis and the corticosteroid doses administered after transplantation. This implicates that the time on dialysis is an important factor in acquiring aseptic necrosis after transplantation. It is concluded that the increase of renal osteodystrophy in the patients treated for a longer period of time with hemodialysis, leads to this higher risk of developing aseptic necrosis after transplantation.

Support for this statement could be found in the study of serum calcium and phosphate before and after transplantation. The fact that aseptic necrosis developed significantly more frequently in patients with a low mean serum calcium in the last year before transplantation and with a low serum phosphate until at least 6 months afterwards could only be explained by assuming a more severe degree of renal osteodystrophy in those patients.

Until the moment corticosteroids are no longer necessary for achieving a successful transplantation, "a low dose regime" of corticosteroids is required in order to decrease the risk of developing aseptic necrosis. Early and careful treatment of renal osteodystrophy in patients with renal failure and later on during hemodialysis treatment, followed by transplantation within 1 1/2-2 years, are at this moment two factors of at least even great importance to achieve a lower incidence of aseptic necrosis of bone after a successful kidney transplantation.