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Osteonecrosis of Femoral Head (ONFH) After Renal Transplantation

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1. Introduction

Approximately 25,000 patients undergo renal transplantation every year worldwide due to end-stage renal disease(ESRD). Renal transplantation is expected to lead to a progressive correction of the established renal bone disease, and osteonecrosis of the femoral head(ONFH) is a common and severe complication in these patients. It induces deformity of the hip joint and reduces the quality of life, especially in the young population ranging from 20 to 50 years old. Total hip replacement is not reasonable in this population due to the finite lifespan of implants. Clinical results suggest that free vascularized fibular grafting(FVFG) can slow or potentially halt the progression of osteonecrosis, it offers an alternative method for preserving the femoral head in younger renal transplant recipients.

2. Clinical backgroud

Chronic renal failure(CRF) and end-stage renal disease(ESRD) are associated with many disturbances of bone structure and metabolism due to deficiency of calcitriol, hypocalcemia, retention of phosphate, metabolic acidosis, secondary hyperparathyroidism. Renal transplantation can improve the metabolism disturbances of ESRD, but osseous complications like osteoporosis, consequent fracture, bone pain and osteonecrosis are not rare. It is reported that up to 40% of renal graft recipients have spontaneous osteoporotic pain. A major obstacle to the investigation of renal osteodystrophy in transplant recipients has been its unpredictable evolution under the multiple biochemical and hormonal influences that regulate mineral metabolism and bone turnover independently. Its course after transplantation depends on persisting abnormalities such as hypercalcaemia, hypophosphataemia and hypomagnesaemia as well as on the type, dose and duration of immunosuppressive medications that are needed to minimize allograft rejection.

2.1 Morbidity of ONFH in the recipients

Osteonecrosis of the femoral head (ONFH), an aseptic and ischemic disease, is especially common in the transplant recipients. Kubo documented femoral head MRI abnormalities of osteonecrosis in 25% of 51 renal allograft recipients; Marston reported 20% of 52 patients and 11% of 103 hips developed ONFH within 1 year after transplantation; Lopez-Ben reported 4%

of 48 patients and three of 96 hips had ONFH within 6 months after renal transplantation; In the study of Lee, ONFH developed in 6.3% of the 237 patients and 4.9% of the 473 femoral heads from 8 months to 16 months after renal transplantation. In the report of Children by Nishiyama *et al*, 141 renal transplants were performed in 129 children(72 boys and 57 girls), aged from 2 to 17 years. Osteonecrosis occurred in seven patients, in the following sites: the femoral head in four children including two bilateral cases: and the femoral condyle in Three children, with two bilateral cases. The mean period from transplantation to the diagnosis of OHFH was 18 months, 75% appeared more than 9 months after transplantation.

2.2 Etipathogenesis

2.2.1 Use of corticosteroids

High doses of corticosteroids are used after renal transplantation to reduce rejection and improve graft survival. They have also been implicated as the major predisposing factor for post-transplant bone loss and osteonecrosis, and It takes a few years to develop osteonecrosis after the start of corticosteroids therapy. Although corticosteroids therapy represents a pathogenetic key factor other immunosuppressive drugs such as cyclosporine, tacrolimus, azathioprine and rapamycin clearly contribute to its prevalence and expression through their pleiotropic pharmacological effects. These drugs have been shown to increase overall bone turnover and/or to stimulate loss of bone mass independently. Long-term glucocorticoid administration and possibly cyclosporine treatment may chronically activate osteoclasts in spongy and/or cortical bone while osteoblast activity is inhibited, and the highest tertiles of cumulative glucocorticoid were significantly associated with BMD loss and osteonecrosis. A prospective study using MRI in renal transplant patients showed the occurrence of ONFH within several months after the initiation of steroid treatment, and a time discrepancy between the occurrence of ONFH and onset of symptom.

2.2.2 Dose-related risk of osteonecrosis

Furthermore, an appreciable dose-related risk of osteonecrosis was also found in patients receiving long-term steroid therapy. Hirota *et al* reported the relationship between ONFH and the daily dosage of steroid (#16.6 mg in terms of prednisolone) or the highest daily dose (#80mg in terms of prednisolone) and concluded that higher steroid dosage per day contributed to increasing the frequency of ONFH in renal transplant patients. In a retrospective study of the medical records of 750 patients who had received a renal transplant during the period of 1968-1995, Lausten showed an 11.2% incidence of symptomatic osteonecrosis with high-dose glucocorticoids(cumulative mean dose of prednisolone 12.5g at 1 year post-transplant) and 5.1% with low-dose(cumulative mean dose of prednisolone average dose 6.5g). This difference in numbers of femoral head necroses was highly significant ($p < 0.005$); The cohort of Kopecky *et al* showed an osteonecrosis incidence of 22%, had a prednisolone equivalent dose of 7±3.25g prednisolone during the first 90 days after transplantation; The cohort of Lopez-Ben *et al* showed an osteonecrosis incidence of 4%, had a slightly lower cumulative steroid dosage (2.1g prednisolone at 3 months after transplantation) compared to previously reported cohorts; Lee *et al* also found a low incidence of ONFH in renal transplantation patients at the time of 1 year post-transplantation, which seems to be related with low cumulative steroid dosage. There is no known threshold dose. In clinical practice, some patients fail to benefit from daily doses as

low as 2.5–7.5 mg of prednisone, whereas daily doses >7.5 mg will definitively induce osteoporosis and osteonecrosis in the majority of patients.

2.2.3 Main mechanism

The mechanism of ONFH after renal transplantation includes: 1. Thrombus due to the steroid-induced hypercoagulable state(Hypercoagulability of plasma was found after 3 months of steroid treatment in previous studies). 2. Reduction of blood flow in bone(Femoral head blood flow was 2-3 fold lower after 2 week high dose steroid treatment, decreased arterial inflow or increased venous outflow resistance can reduce intraosseous blood flow) 3. Osteoporosis of femoral(Steroid can decrease the absorption of calcium from intestine and increase its elimination via the kidneys. Direct and indirect effects on PTH secretion, changes in bone protein matrix, increased osteoclastic activity, and decreased protein synthesis all lead to a reduction in bone mass after renal transplantation, inhaled corticosteroids in doses above 1.5 mg/d may be associated with a significant reduction in bone density). 4. Metabolism disorder. 5. Fat embolism of femoral head. 6. Rise of intraosseous pressure(In the rigid intraosseous compartment, growth of fat cells may cause a rise in intraosseous pressure, and thereby compress the thin-walled sinusoids, with a subsequent decrease in bone blood flow). 7. Degenerative changes of the hip capsule(Degenerative changes in the arteries and arterioles of the capsule of the hip and the femoral head have been found in cadavers of renal transplant patients without clinical hip symptoms. There was thickening of the intima, gross diminution in the number and calibre of the vessels in the arteries of the femoral head and infarcts of subchondral bone).

2.2.4 Other risk factors

The type of donor, dialysis duration, acute rejection rate, and postoperative weight gain. The age of the graft recipients also matters. An age of less than forty years is a risk factor for osteonecrosis of the femoral head.

2.3 Contradiction during the treatment

ONFH continues to be a difficult problem to manage, especially in renal transplant recipients. Both the patients and surgeons were concerned about changes of renal function and survival of the graft. They paid little attention to the hip joint, although early signs of osteonecrosis were present. High doses of steroids were used in a continuous manner, neglecting the abnormal joint function, which hastened the deterioration of the femoral head. ONFH was diagnosed at a mean of 3.5 years after transplantation, it can progress to severe osteoarthritis and seriously impair the life quality of transplant recipients. Early hip joint symptoms, including progressing hip pain and joint dysfunction, always appear 9 to 19 months after transplantation, But in most of the clinical cases, severe joint pain and irreversible collapse of the femoral head had already developed when the diagnosis was established. Furthermore, steroid-induced ONFH following transplantation tends to have larger necrotic areas, and bilateral involvement is more common than unilateral involvement. the natural history of femoral head osteonecrosis has shown evidence that a large majority of clinically diagnosed cases will progress to femoral head collapse. The treatment of ONFH depends on the staging and severity of the clinical symptoms.

3. Therapy methods

3.1 Core decompression and THA

Joint-preserving operations like core decompression cannot arrest the progression of the disease effectively. Total hip replacemen(THA)t is also unsuitable for younger patients because of their higher activity level and longer remainder of life. So Osteonecrosis of the femoral head continues to be a difficult problem to manage, especial in the patient with various kinds of renal diseases(such like IgA nephropathy, focal segmental glomerular sclerosis, membranous nephropathy, mesangial proliferative glomerulonephritis, crescent glomerulonephritis, lupus nephritis, minimal change nephropathy and renal transplantation after end-stage renal diseases). Many patients with renal diseases inevitably lose the ability to live independently due to advanced stages of osteoarthritis.

3.2 FVFG

FVFG showed favorable outcomes. Compared with core decompression of femoral head, FVFG had a significantly lower conversion rate to total hip arthroplasty(stage II and III hips), because it can enhance the revascularization of bone tissue and arrest the progression of the necrosis. It is also an alternative method for younger patients without severe osteoarthritis of the hip joint.

3.2.1 Advantages of FVFG

The advantage of FVFG lies in the combination of femoral head decompression(Extensive decompression of the femoral head along with removal of necrotic bone theoretically interrupts the cycle of increased intraosseous pressure and ischemia and allows for revascularization of the femoral head), removal of necrotic bone, introduction of osteoinductive cancellous bone(Filling the defect with fresh cancellous bone provides both osteoinductive and osteoconductive stimulation of healing), and vascularized cortical bone support of the subchondral surface(The vascularized fibula provides a viable cortical bone strut to support the subchondral bone from collapse and further enhances the revascularization process). This procedure may benefit young patients with more advanced osteonecrosis of the femoral head by halting progression of collapse, prolonging reduction of symptoms, and postponing total hip replacement.

3.2.2 Clinical application of FVFG

With the emergence of microsurgical techniques, Judet *et al* first treated ONFH with FVFG in the late 1970s. The long-term results cover 68 hips in 60 patients with 18 of these classified as early failures requiring conversion to THA. The remaining 50 hips were followed on average for 18 years. Thirty-five hips scored good or very good, which corresponds to a 52% success rate, the data clearly show an increase in good results for patients younger than 40 years, and an increase in the rate of failures for patients older than 40 years. Specifically, of the patients younger than 40 years, 80% had good and very good results, whereas of the patients between 40 and 50 years, only 57% had good and very good results. After systemic research and long-term clinical study, Urbaniak *et al* improved the surgical technique. The results for 103 consecutive hips(eighty-nine patients) that had been treated with FVFG because of symptomatic osteonecrosis of the femoral head were reviewed in a prospective

study. total arthroplasty had been performed in thirty-one hips: five (23 per cent) of the twenty-two that were in stage III; seventeen (43 per cent) of the forty that were in stage IV; and seven (32 per cent) of the twenty-two that were in stage V. Harris hip scores had improved at the latest follow-up evaluation, compared with the preoperative values ($p < 0.001$). For the stage-II hips, the average score improved from 56 to 80 points; for the stage-III hips, from 52 to 85 points; for the stage-IV hips, from 41 to 76 points; and for the stage-V hips, from 36 to 75 points. 59 percent of the hips did not limit or only slightly limited the patient's ability to carry out daily activities, and 62 percent did not limit or only slightly limited the patient's ability to work. FVFG had decreased the need for pain medication for 86 percent of the hips that had not been subsequently treated with an arthroplasty. Regardless of whether or not a subsequent arthroplasty was done, 81 per cent of the patients (81 per cent of the hips) were satisfied with their decision to have fibular grafting.

FVFG became widely performed in their clinical activities. Some other clinical research also showed good results. Zhang *et al* treated 56 hips in 48 patients with FVFG and followed patients for a mean duration of 16 months. Roughly 69.6% of femoral heads showed improvement on radiographs, and the Harris hip scores showed improvement ranging from 11-13 points. Most patients had full weight-bearing ability and took part in their daily activities. Aldridge *et al* reported an 88% success rate associated with FVFG in the femoral heads without collapse and a success rate of 78% with subchondral collapse. The results showed that FVFG is the most promising technique because it had satisfactory mid-term and long-term outcomes. Fibular grafts have also been proven to be alternative for the post-collapse stage of ONFH, It is also a worthwhile procedure in patients with postcollapse osteonecrosis. 188 patients (224 hips) who had undergone free vascularized fibular grafting, between 1989 and 1999, for the treatment of osteonecrosis of the hip that had led to collapse of the femoral head but not to arthrosis. The mean preoperative Harris hip score was 54.5 points, and it increased to 81 points for the patients in whom the surgery succeeded; 63% of the patients in that group had a good or excellent result, Patients with postcollapse, predegenerative osteonecrosis of the femoral head appear to benefit from FVFG, with good overall survival of the joint and significant improvement in the Harris hip score. FVFG is a well accepted treatment option for all symptomatic stages of the disease ,with proper patient selection, middle and long-term outcomes appear promising. FVFG continues to be a primary treatment option to provide relief of symptoms and preserve bone stock, especially in the younger patient population.

3.2.3 Attampts on the renal transplant recipients

FVFG has been rarely systematically reported in renal transplant recipients, although ONFH after renal transplantation is not rare in the clinical work. Recipients with renal insufficiency and unstable general conditions cannot withstand the excessive blood loss and traumatic stress of a hip operation. Postoperative renal graft dysfunction, severe anemia, electrolyte disorder, and infection are life-threatening complications. Therefore, laboratory indices, including the HB, WBC, ESR, BUN, SCr, UA, electrolyte, 24 hours urine volume, and urine protein quantity, are indispensable. In addition, the CRP and ESR should also be included as a nonspecific marker of the activation of the immune system in order to provide early signs of postoperative graft dysfunction and infection. Furthermore, the surgery should be rapid and less invasive. The use of toxic renal medicine should be avoided as well. Guo report three renal transplant recipients with ONFH who underwent FVFG in the

orthopedics department of Shanghai Sixth Poeple's Hospital. Of the three cases, two cases showed radiographic improvement, one case showed radiographic unchanged. All the three cases have been living in good health and are satisfied with their joint function. The hip joint pain was significantly relieved and joint motion was also improved, The Harris hip score elevated 22 points in average, and the Visual Analogue Scale (VAS) was decreased by 37.3 points. Their quality of life has been greatly improved and the gait can return to normal after positive rehabilitation training. The patients were able to walk without aid, even engaged in sports. After operation, the patients returned to full activities with a better quality of life due to normal joint and kidney function. The follow-up results demonstrated that FVFG is safe, effective, and feasible for transplant recipients without serious renal graft dysfunction, anemia, or other systemic diseases. However, the safety of the operation should also be attributed to proficient surgical technique, meticulous laboratory monitoring, and deliberate postoperative supportive treatment.

3.2.4 Indication discussion

According to our previous experience, indications for using FVFG to treat ONFH in patients after the renal transplantation include: 1) A patient younger than 50 years who is not suitable for total hip replacement; 2) Severe hip pain that greatly impairs daily activity; 3) Necrosis of the femoral head less than Steinberg stage V (osteoarthritis stage); 4) The recipient's general physical condition is stable without renal graft dysfunction, serious anemia, metabolic disorder, or any other systemic diseases; 5) The recipient is active and in need of a high quality of life; 6) To take the safety of operation into account, FVFG ought to be performed at least one year after transplantation.

4. Clinical example

A 39-year-old man who was diagnosed with IgA nephropathy by renal biopsy and histopathological examination in January 1998. The disease developed to chronic renal failure six years later. The patient was maintained on hemodialysis for 10 months until unilateral renal transplantation in May 2005. He received steroid therapy for 18 months after the operation. The accumulative dose of corticosteroids was 7.5g (converted to prednisone dose). Tacrolimus (FK-506) 15mg per day and MMF 2.0g was also taken each day at the same time. He visited our hospital in November 2006 because of severe hip joint pain on the left side. The symptom became aggravated quickly, and the patient had to take 0.6mg Ibuprofen per day to maintain his daily activities. He was diagnosed with left side ONFH upon hip X-ray and MRI (classified as Steinberg stage III, Fig 1 a, b). A physical exam revealed a gait abnormality, deep inguinal region pain, positive Thomas sign, and Trendelenburg sign on the affected side. A decreased range of motion occurred in abduction and flexion. The Harris hip score was 72 points, and the VAS pain score was 80 points. All routine laboratory examination results were normal upon admission (shown in Table 1). FVFG on the left side was performed uneventfully one week later. The laboratory exam showed no significant change, except for a slight elevation of the WBC to 11.2×10^9/L on postoperative day 1. The body temperature rose to 37.9°C. The WBC returned to 8.6×10^9/L on day 3 and 7.4×10^9/L on day 7 after antibiotic treatment (intravenous Cefuroxime 3.0g drip bid for 3 days), and the patient's temperature also returned to normal. The patient was discharged within 2 weeks in good health. No signs of infection or renal graft dysfunction

were discovered during the 1 year and 8 months of follow-up. The latest radiograph results showed improvement (Fig 1 c). The left joint pain and stiffness were significantly relieved. A daily pain-killer was no longer needed. The patient's gait also returned to normal after positive rehabilitation training. He returned to his full activities with a better quality of life due to normal joint and kidney function. The Harris hip score rose to 89 points, and the VAS pain score decreased to 28 points.

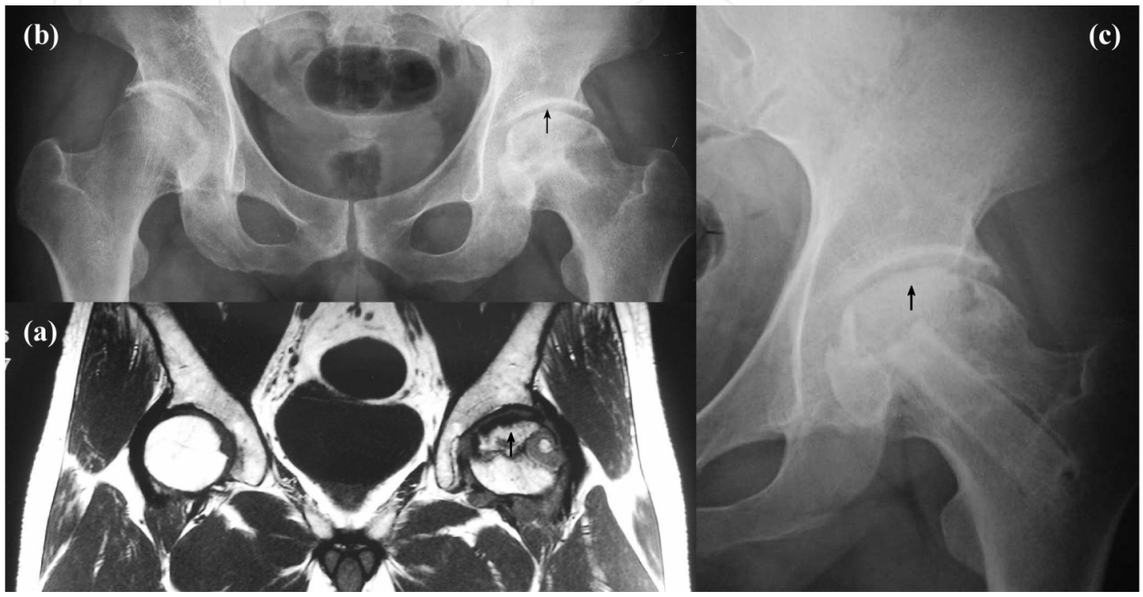

Fig. 1. (a) Preoperative radiograph (b) T1-weighted MRI (c) Radiograph 1 year and 8 months after FVFG showed revascularization of the necrosis area. The femoral head did not collapse.

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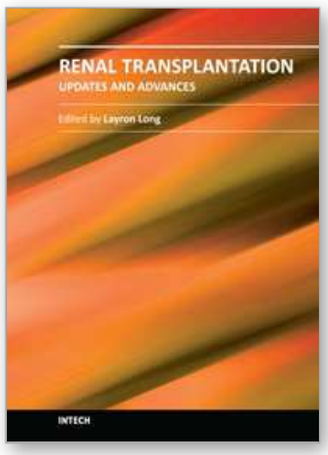

Renal Transplantation - Updates and Advances

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This book presents a nice international compilation of scholarly papers and chapters which address the latest advances in renal transplant surgery. These works cover a variety of topics; the last advance and success of renal transplant science: biochemistry, immunology, molecular genetics, pharmacology - pharmacogenetics, pediatric transplant and a few rare uropathies that warrant organ replacement.

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