

Immunosuppressant-Related Hip Pain After Orthotopic Liver Transplant

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Abstract

Objectives: Immunosuppressant-related hip pain can greatly affect a patient's mobility and increase the number of total hip arthroplasties. We investigated risk factors and causes of hip pain after orthotopic liver transplant.

Materials and Methods: The medical records of 175 adult orthotopic liver transplant patients, who were followed-up for more than 2 years, were retrospectively reviewed. Data collected from the records included primary disease, medications, biochemical results, Child-Turcotte-Pugh score, death, rejection, and complications related to liver transplant.

Results: A total of 11 patients (6.3%) complained of hip pain, which was diagnosed as calcineurin-inhibitor-induced pain syndrome in 4 patients (2.3%), osteonecrosis of the femoral head in 3 patients (1.7%), and osteoporosis in 2 patients (1.1%). The incidence of calcineurin-inhibitor-induced pain syndrome was related to the dosage of tacrolimus ($P > .05$) but independent of methylprednisolone use. The occurrence of osteonecrosis of the femoral head was independent of the dosage and early withdrawal of methylprednisolone ($P > .05$). Patients with methylprednisolone withdrawal within 6 months

had significantly longer survival than those using methylprednisolone for more than 6 months (50 ± 15 vs 41 ± 18 mo; $P = .007$).

Conclusions: Calcineurin-inhibitor-induced pain syndrome and osteonecrosis of the femoral head are main causes of hip pain in adult orthotopic liver transplant patients. Osteonecrosis of the femoral head was not common, but the incidence of hip pain owing to calcineurin-inhibitor-induced pain syndrome was relatively high in orthotopic liver transplant patients. Early withdrawal of methylprednisolone could benefit the patients' survival.

Key words: Calcineurin-inhibitor-induced pain syndrome, Hip pain, Immunosuppressant, Osteonecrosis of femoral head, Osteoporosis

Introduction

Use of immunosuppressants is essential after solid-organ transplant. Over the past few decades, while glucocorticoids have remained an important part of initial and maintenance immunosuppression, other immunosuppressants have been developed; especially those acting on immunophilins such as cyclosporine, tacrolimus, and sirolimus have greatly reduced the incidence of rejection. While immunosuppressants prevent the rejection of transplanted organs and tissues, they also cause various adverse events. Immunosuppressant-related hip pain can greatly affect a patient's mobility and increase the chances of hip arthroplasty.

Hip pain is most often a manifestation of osteoporosis and osteonecrosis. The prevalence of osteoporosis varies from 17.5% to 30%,^{1,2} which is

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less in femoral neck than in other parts of body.³ It is multifactorial in its cause, which may result from existing liver diseases or immunosuppression therapy. The prevalence of osteonecrosis of the femoral head (ONFH) in patients who have undergone solid-organ transplant varies from 1.5% to 24%, depending on primary disease, immunosuppression therapy, age, and sex. Marston and associates reported the incidence of ONFH as 20% one year after renal transplant.⁴ In other studies, however, the incidence of ONFH was as low as 1.5% to 4.6% in liver, kidney, and heart transplant recipients.⁵⁻⁸ In addition, some rare conditions also should be considered, including calcineurin-inhibitor-induced pain syndrome (CIPS). The relation between calcineurin inhibitors and bone pain was first reported by Bouteiller and associates in 1989,⁹ and it was named *calcineurin-inhibitor-induced pain syndrome* by Grotz and colleagues in 2001.¹⁰ The prevalence of CIPS is 1% to 17%, mostly occurring in renal transplant recipients.¹⁰⁻¹⁵ The mechanism of CIPS is unknown because it is a rare syndrome, and there is a lack of systematic study about it.

Over the past decade, the number of liver transplants performed worldwide has increased. The development of other immunosuppressants allows the early withdrawal of glucocorticoids, which may affect the outcome of immunosuppression after liver transplant, including the manifestation of adverse events. Although the techniques of transplant and posttransplant treatment in China have been developed in line with Western countries, the immunosuppressant-related hip pain after liver transplant has never been investigated in Chinese adult patients. Therefore, we conducted a retrospective study to investigate the risk factors and causes of hip pain after orthotopic liver transplant to provide useful information for clinical practice.

Materials and Methods

The medical records of patients who underwent orthotopic liver transplant at the Third Affiliated Hospital of Sun Yat-sen University between January 2004 and December 2007 were retrospectively studied in January 2010. This time was selected to allow a minimum 2-year postoperative follow-up. Patient inclusion criteria included the following:

over 18 years of age, first-time liver transplant, more than 2 years follow-up, without pretransplant osteoarticular disease, corticosteroid exposure, and excessive alcohol intake. The study protocol was approved by the University Ethics Committee and has been performed in accordance with the ethical standards put forth in the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. The use of the transplanted organs was approved by the ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, all organ donations were voluntary, and all donors and/or their next of kin provided written consent for organ donation.

Data collected from the records included primary disease, medications (preoperative, perioperative, and postoperative use of glucocorticoids and other immunosuppressants), laboratory examination results such as serum alkaline phosphatase, creatinine, urea nitrogen, cholesterol, triglycerides, calcium, total bilirubin and direct bilirubin levels, clinical outcome including death and rejection, Child-Turcotte-Pugh (CTP) score, and complications related to liver transplant. When patients returned for routine follow-up, they were specifically asked whether they had pain or other problems with their hips or other joints. If there was obvious deep, throbbing pain; a clinical examination, conventional radiographs, and magnetic resonance imaging were performed.

Osteoporosis and osteonecrosis were diagnosed according to the clinical guidelines of American College of Rheumatology. Osteonecrosis of the femoral head was graded according to Ficat and Arlet classification (grades I to IV).¹⁶ The diagnosis of CIPS was made based on progressive pain in the joints or muscles after transplant related to calcineurin inhibitors; no abnormalities of joints revealed by conventional radiographs; magnetic resonance imaging could show bone marrow edema in the femur condylus; pain owing to obvious clinical diseases such as osteoporosis and osteonecrosis had been excluded; pain was only relieved by withdrawal of calcineurin inhibitors, not anti-inflammatory drugs.

The posttransplant immunosuppression regimen consisted of methylprednisolone (MP) and a calcineurin inhibitor such as tacrolimus and cyclosporine. The dosage of tacrolimus was

adjusted according to the desired serum level, targeted to a concentration of 10 to 15 ng/mL during the first month, and then slowly reduced to attain peak levels of 10 to 12 ng/mL at 6 months and 5 to 10 ng/mL at 1 year and thereafter. In a few cases, monoclonal antibodies such as daclizumab were used for induction. In patients with renal failure, toxicities associated with calcineurin inhibitors, or CIPS, the dosage of tacrolimus was reduced first. If the condition did not improve, tacrolimus was replaced by the combination of mycophenolate mofetil and sirolimus. The cumulative dosage of tacrolimus was calculated at 12 months and 24 months.

Glucocorticoids are still considered a first-line treatment in posttransplant immunosuppression. All patients were given preoperative intravenous MP 1000 mg/d or 500 mg/d, which was rapidly tapered to 40 mg/d within 7 days after the transplant. Beginning on postoperative day 7, a 48-mg dose of MP was given orally and then gradually tapered to 4 to 8 mg/d over 12 days. This dosage was maintained for 3 to 12 months according to the primary diseases and patient's physical condition. The cumulative dosage of MP was calculated at 6 and 12 months.

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 17.0, IBM Corporation, Armonk, New York, USA). Quantitative data are expressed as means \pm SD. The difference between 2 groups was analyzed by the Welch *t* test or Mann-Whitney *U* test. Qualitative data are expressed as a percentile and subjected to the Fisher exact test. Pearson's correlation coefficient analysis or Kruskal-Wallis test was performed to determine the correlation between hip pain and the use of corticosteroids and other immunosuppressives. Multivariate analysis was performed to determine risk of hip pain. Values for *P* less than .05 were considered statistically significant.

Results

During the study, 175 liver transplant recipients were followed-up in our hospital for more than 2 years, including 159 men and 16 women (mean age, 47 ± 11 years; age range, 19-72 y; mean survival,

46 ± 16 mo; range, 24-72 mo). The primary diseases for liver transplant were hepatitis B-related liver cancer, cirrhosis, and liver failure in 150 patients (85.7%) and other diseases including hepatocellular carcinoma, primary biliary cirrhosis, Wilson disease, and primary sclerosing cholangitis in 25 patients (14.3%). All patients used MP as a fixed part of the initial dosage and maintenance immunosuppression; 61 patients (34.9%) withdrew MP within 6 months, and 114 patients (65.1%) used MP up to 12 months.

Eleven patients complained of hip pain, which was diagnosed as CIPS in 4 patients (2.3%), ONFH in 3 patients (1.7%), osteoporosis in 2 patients (1.1%), simple muscular pain in 1 patient (0.6%), and metastatic cancer in 1 patient (0.6%). All were treated with MP and tacrolimus. In 4 patients with CIPS, severe pain occurred in the hip and other parts of the lower limbs within 3 months after transplant, which could not be relieved by anti-inflammatory drugs or reducing the dosage of tacrolimus. Radiographic examination did not reveal any abnormality in the lower limb joints. Magnetic resonance imaging scans revealed normal femoral head in 2 patients (Figure 1A) and unilateral bone marrow edema in the femoral head in other 2 patients (Figure 1B). After tacrolimus was withdrawn, the pain finally eased. Compared with those without CIPS, the cumulative dosage of tacrolimus in CIPS patients was significantly reduced, but no differences were noted in terms of age, CTP score, biochemical characteristics, and survival time between the 3 groups (*P* > .05) (Table 1). Furthermore, a positive correlation was found between hip pain and the cumulative dosage of tacrolimus in CIPS patients (12 months: $r=0.300$, *P* = .001; 24 months: $r=0.280$, *P* = .002).

Osteonecrosis of the femoral head was ultimately diagnosed in 3 patients (1.7%) an average of 14 ± 6 months after transplant (range, 10-21 mo). All of them had bilateral ONFH (Figure 1C and Table 2). The immunosuppression regimen consisted of MP and tacrolimus in all 3 patients and concurrent cyclosporine or daclizumab in 2 patients. Methylprednisolone was withdrawn in 6 months in 2 patients. No differences were found in terms of cumulative dosages of MP (6 mo: 3553 ± 501 mg vs 3147 ± 884 mg; *P* = .126; 12 mo: 4067 ± 572 mg vs 3588 ± 1287 mg; *P* = .123) between ONFH patients and non-ONFH patients. There was

Figure 1. Cross-Sectional MRI Image of the Femoral Head

(A) Normal femoral head: MRI T1W1 image showing even signals in the patient with simple musculoskeletal pain; (B) bone marrow edema in patients with CIPS: MRI T1W1 image showing low signal in the right femoral head (indicated by arrow); (C) osteonecrosis of femoral head: MRI T1W1 image showing bilateral irregular low signal lines (indicated by arrows).

no correlation between the incidence of ONFH and the dosage and early withdrawal of MP ($P > .05$).

We further compared patients who withdrew MP within 6 months and those who had MP more than 6 months (total cumulative dosage of MP: 2951 ± 864 mg vs 4485 ± 928 mg; $P > .0001$). The incidence of CIPS, osteoporosis, and ONFH was not significantly different between the 2 groups ($P > .05$), suggesting that the early withdrawal of MP

Table 1. Comparison of Patients With and Without Calcineurin-Inhibitor-Induced Pain Syndrome (CIPS)

	Non-CIPS (n=171)	CIPS (n=4)
Age at OLT (y)	47 ± 11	39 ± 10
Survival time (mo)	46 ± 17	52 ± 2
CTP score	14 ± 3	11 ± 1
Total bilirubin (μmol/L)	212.64 ± 258.37	362.10 ± 311.18
Direct bilirubin (μmol/L)	112.28 ± 149.35	204.93 ± 118.51
Alkaline phosphatase (U/L)	118.52 ± 78.95	112.75 ± 34.21
Creatinine (μmol/L)	103.80 ± 30.28	69.55 ± 19.44
Urea nitrogen (mmol/L)	6.35 ± 3.40	3.36 ± 1.38
Cholesterol (mmol/L)	2.82 ± 1.84	1.18 ± 1.25
Triglycerides (mmol/L)	0.89 ± 0.73	0.65 ± 0.55
Calcium (mmol/L)	2.30 ± 0.33	2.27 ± 0.25
Cumulative doses of tacrolimus		
12-month (mg)	1451 ± 626	349 ± 332†
24-month (mg)	2458 ± 1173	349 ± 332

Abbreviations: CTP, Child-Turcotte-Pugh; OLT, orthotopic liver transplant
† $P > .01$ compared with patients without CIPS

did not reduce the occurrence of CIPS, osteoporosis, or ONFH. However, the patient withdrawing MP within 6 months had a significantly longer survival time than those using MP for more than 6 months (50 ± 15 vs 41 ± 18 months; $P = .007$); however, the mortality rate was not significant different (9.8% vs 15.8%; $P = .356$).

Discussion

This is the first study to investigate the incidence of hip pain and related risk factors in adult patients after orthotopic liver transplant. We found that the main causes of hip pain were CIPS, ONFH, and osteoporosis in this cohort of patients without pre-existing osteoarticular disease, corticosteroid exposure, and excessive alcohol intake.

The mechanism of CIPS is poorly understood. Lucas and associates¹¹ studied 26 renal transplant patients who had isolated musculoskeletal pain owing to cyclosporine use and suggested that the interaction between cyclosporine and glucocorticoids, and the toxicity of cyclosporine metabolites, may contribute to CIPS. Grotz and colleagues¹⁰ hypothesized that calcineurin inhibitor-induced vascular disturbance might lead to an increased permeability of bone marrow vessels with consecutive bone marrow edema. However, bone marrow edema is a nonspecific change of CIPS because it can also occur in osteonecrosis, a joint disorder caused by wear and tear, osteoporosis, ischemia, and tumors.

Nevertheless, specific changes of CIPS are lacking. The diagnosis of CIPS is based mainly on exclusion of pain owing to other causes and its correlation to

Table 2. Characteristics of Patients With ONFH

Patient	Sex	Age	Reason for OLT	Imm [†]	Months Post-OLT	Duration of MP Treatment (mo)	ONFH	Treatment
1	M	44	Cirrhosis, HBV	MP, Tac, CsA	11	6	Bilateral	Total hip arthroplasty (right), core decompression and bone grafting (left)
2	M	40	HCC, HBV, cirrhosis	MP, Tac, Dac	10	12	Bilateral	total hip arthroplasty (right), core decompression and bone grafting (left)
3	M	46	HCC, HBV, cirrhosis	MP, Tac	21	6	Bilateral	Pharmacologic treatment

Abbreviations: CsA, cyclosporine A; Dac, daclizumab; HBV, Hepatitis B; HCC, hepatocellular carcinoma; M, male; MP, methylprednisolone; OLT, orthotopic liver transplant; ONFH, osteonecrosis of the femoral head; Tac, tacrolimus
[†]Immunosuppressive regimen

the use of calcineurin inhibitors. In this study, patients with pre-existing osteoarticular disease, corticosteroid exposure, and excessive alcohol intake have been excluded. Although long-standing cholestasis owing to liver diseases may remain, the diagnosis of osteoporosis and osteonecrosis also has been excluded by radiograph and magnetic resonance imaging scans in 4 patients suspected with CIPS. Their hip pain was closely related to the use of tacrolimus and not responsive to anti-inflammatory drugs. As a result, the diagnosis of CIPS was made. Although CIPS is characterized by symmetric pain mainly involving the ankles, feet, and knees (because they are subjected to greater venous blood pressure in standing position),^{10,17} it also can occur in the femur as reported by Nishikawa and associates.¹³ Previously, CIPS cases were rarely reported in liver transplant patients. In our study, the incidence of CIPS owing to tacrolimus treatment was 2.3%, which is relatively high. It is not clear whether this is related to tacrolimus or liver dysfunction. Jain and colleagues¹⁸ reported that patients with hepatic dysfunction had a longer half-life of tacrolimus (corresponding to a lower clearance rate and higher trough plasma concentration); and the presence of CIPS is correlated to a high blood concentration of calcineurin inhibitors.^{12,19} This may explain why the incidence of CIPS is high in our present study involving OLT patients; hence, specific attention should be paid to the application of tacrolimus in patients with liver dysfunction in clinical practice.

In our study, the incidence of ONFH was only 1.7%, and the diagnosis was made about 1 year after transplant. It is not related to the cumulative dosage of MP and tacrolimus or the early withdrawal of MP. Our findings are consistent with the reports by

others,^{4,8,20-23} suggesting that symptomatic ONFH is rather uncommon in this cohort of liver transplant patients on current immunosuppressive protocols. The underlying mechanism of osteonecrosis in liver transplant recipients is complex, which may be related to corticosteroid use, hypercoagulable state, or hypofibrinolysis.⁵ Many patients with liver failure may have multifactorial metabolic bone disease before the transplant. Pre-existing liver disease and alcohol excess may precipitate the occurrence of ONFH. We have excluded patients with alcoholic liver disease; therefore, the prevalence of ONFH is no doubt lower in our study than in others.

The relation between osteonecrosis and corticosteroid dosage is controversial. Some researchers have found a significant decrease of ONFH in transplant patients who were treated with a reduced dosage of corticosteroids compared with those treated with traditional protocols.²⁴ Others, however, have demonstrated that induction of osteonecrosis owing to corticosteroid use is dose-independent.^{5,25} In our study, we also found that the induction of ONFH was not correlated with the cumulative dosage and early withdrawal of MP, confirmed by a dosage-independent effect of MP on the occurrence of ONFH in Chinese adult patients after liver transplant.

Several factors contribute to osteoporosis after liver transplant including factors associated with chronic liver disease, per se, and those related to immunosuppression such as corticosteroids. Glucocorticoids can reduce bone formation and increase bone resorption, thereby leading to osteoporosis.^{26,27} The mechanisms by which these effects are achieved are complex, including inhibition of osteoblast differentiation and activity,

the latter effect being mediated by stimulation of apoptosis.²⁸ Corticosteroids also reduce osteoclast apoptosis, thus increasing bone resorption and increasing osteocyte apoptosis, an effect implicated in developing avascular necrosis.²⁹ Although corticosteroid dosage has not been shown to be related to fracture risk in liver transplant recipients, several studies have shown a corticosteroid dose-dependent effect on bone loss in patients undergoing renal, cardiac, and lung transplant.³⁰⁻³² Bone loss may occur soon after corticosteroid initiation and is greatest during the first year.³³

In recent years, development of new immunosuppression agents has allowed for early steroid withdrawal after organ transplant, which may reduce the incidence of osteoporosis and osteonecrosis.^{24,34} In our study, tacrolimus was used in most patients, which allowed nearly half the patients to withdraw MP within 6 months after transplant, and thereby dramatically reduce the dosage of MP. However, we have only 2 cases of osteoporosis. It is not powerful enough to perform any statistical analysis; thus, it is hard to tell whether such low incidence of osteoporosis in our study is due to early withdrawal of corticosteroid use. Studies in animal models show that other immunosuppressants such as cyclosporine and tacrolimus could reduce bone mass,³⁵ but such an effect is difficult to identify in humans because these immunosuppressive agents are always combined with corticosteroids.

In our cohort of patients, the male sex was predominant. This may reflect the present condition of liver transplants in China, because men usually have stronger financial support than women in Chinese society. Additionally, we found that survival time in patients withdrawing MP within 6 months was longer than those who used MP for more than 6 months (but the rejection rate was similar between 2 groups of patients), suggesting that early withdrawal of MP will not affect rejection. It can certainly prolong a patient's life, probably via reducing the adverse events of corticosteroid treatment.

The present study has certain limitations owing to the relatively small number of patients with ONFH. Also, we did not measure bone mass, thereby underestimating the effect of MP on this cohort of patients. Nevertheless, this is the first study about immunosuppression-related hip pain

in Chinese OLT patients. It provides important information about the symptomatic ONFH and CIPS with current individual treatment, which is helpful for our clinical practice.

Conclusions

Calcineurin-inhibitor-induced pain syndrome and ONFH are main causes of hip pain in adult OLT patients. Osteonecrosis of the femoral head was uncommon, but the incidence of hip pain owing to CIPS was relatively high in OLT patients compared with other studies. Early withdrawal of MP could benefit patient survival.

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