ASPECTS OF CURRENT MANAGEMENT

Total hip replacement in renal transplant patients

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Avascular necrosis of the femoral head creates considerable morbidity in successful renal transplant recipients who are generally young and expect active lifestyles. Total hip replacement is considered the treatment of choice in these patients, but surgeons may be wary because of a supposed increase in the risk of infection and other complications.

A review of the literature reveals that cemented hip arthroplasty provides good to excellent functional outcomes for renal transplant patients. Most authors have found that the risk of infection is not increased despite chronic immunosuppression, but the rates of general complications are and should be anticipated and treated. There is a high rate of early failure in these patients because of their young age and diffuse osteopenia as a result of secondary hyperparathyroidism related to the underlying renal disease and chronic steroid use. Recent studies have found that despite decreased bone stock in these patients, porous-coated prostheses are not contraindicated.

Renal transplantation is the most common solid organ transplant operation in the United States, where approximately 12,000 successful transplants are performed annually.¹ This success depends upon the use of corticosteroids and immunosuppressants such as azathioprine and cyclosporine.²,³ Renal transplant patients require lifelong immunosuppression, placing them at increased risk of infection, malignancy and serious side effects on numerous organ systems, including the musculoskeletal system. The major orthopaedic sequelae of the chronic use of steroids is avascular necrosis (AVN) in major joints, particularly involving the femoral head.⁴,⁵

As these patients are frequently under 40 years of age AVN of the femoral head creates significant morbidity. The overall morbidity will increase as more patients are transplanted successfully.⁶ As end-stage AVN of the femoral head usually requires total hip replacement (THR), in these younger patients subsequent revision procedures may be required. Moreover, as renal transplant patients are on life-long immunosuppressant therapy, the increased risk of infection must be considered. This article reviewing AVN of the femoral head in renal transplant patients examines treatment options, particularly focusing on THR and its complications.

Avascular necrosis of the femoral head

Although the femoral head is most commonly involved and causes the greatest morbidity,⁶,⁷ AVN in renal transplant patients can affect the femoral condyles, tibial plateau, talus, and humeral head. Its incidence in those patients ranges between 3% and 41%.⁸ Bilateral hip disease is characteristic, seen in up to 85% of affected patients.²,⁷,¹² Renal transplant patients are five times more likely to require THR than the general population.⁴,¹³,¹⁴

In the pathogenesis of AVN it is thought that abnormally elevated lipid levels lead to microemboli and endothelial cell changes causing venous stasis, an increased intra-osseous pressure and bone necrosis.⁵,⁸ In renal transplant patients, the ischaemia occurs very early, often within 12 weeks of transplantation.¹⁵,¹⁶ Symptoms may not present until later, but most patients are diagnosed within two years.¹⁷ African-Americans are especially at risk of AVN of the femoral head. It is thought that this could be caused by poor HLA-typing and the need for more episodes of pulse-dosed steroids to combat acute rejection.¹³,¹⁸

Patients who develop AVN of the femoral head complain initially of pain, particularly in the groin.⁵ As the disease progresses, hip movement diminishes, rest and night pain develop and walking is severely affected.⁵,¹² Radiographs may show diffuse porosis, sclerosis, or cyst formation as well as subchondral lucency and collapse (Fig. 1). Extensive degenerative changes in the femoral head and acetabulum denote severe and end-stage disease.
As radiographs may also initially appear normal, MRI may be the best method for the early diagnosis of AVN. Changes may be seen as early as two weeks post-transplant and critical changes by 12 weeks (Fig. 2). However, early changes on MRI are not necessarily indicative of disease progression. With the success of MRI in diagnosis, changes on MRI are now incorporated in the staging systems for AVN. Spectrum emission computerised tomography scanning may play an adjunctive role. Ryu et al reported that MRI was only 66% sensitive in diagnosing AVN of the femoral head whereas spectrum emission computerised tomography was 100% sensitive. The reason for this may be a decrease in renal function in transplant patients allows an increased uptake of bisphosphonate in diseased regions, which is highly detectable by spectrum emission computerised tomography. If available, therefore, bone spectrum emission computerised tomography is recommended if MRI is negative.

Immunosuppression

In attempting to clarify risk factors for steroid-induced AVN of the femoral head, some authors have found that high daily doses are a major contributing factor. Others feel that the number of ‘pulse-dose’ episodes are more critical. As soon as possible, dosage should be reduced to maintenance levels. When the dosage is kept below 15 mg to 20 mg of total steroid per day, the risk of AVN of the femoral head is less than 3%. Stopping or decreasing steroids after AVN of the femoral head is established does not, however, prevent progression.

Newer immunosuppressants such as cyclosporine A, azathioprine, and tacrolimus were developed in order to lessen rejection and combat the side effects of corticosteroids. Cyclosporine A when used with steroids significantly decreases the risk of AVN of the femoral head in renal transplant patients. Tacrolimus was even more effective. These new immunosuppressants decrease the number of acute rejection episodes and reduce the requirement for pulse-dosed steroid treatments.

Treatment of avascular necrosis of the femoral head

The many treatment options include conservative therapy, core decompression with or without vascularised fibular graft or porous trabecular metal implant, proximal femoral osteotomy, trap-door grafting, hip resurfacing, hemiarthroplasty, and THR. Bisphosphonates can reduce the progression and collapse in established AVN, as well as preventing steroid-related osteoporosis, thereby increasing the time until surgery may be needed. Statins or hydroxyethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor have been suggested by Abbot et al as prophylaxis against AVN of the femoral head. These drugs are thought to decrease or halt the hyperlipidemia secondary to steroid use that can lead to ischaemia and necrosis of the femoral head. Demirors et al recommend early surgical intervention in renal transplant patients as there is an extremely high failure rate of 97% associated with conservative measures.

Core decompression is a mainstay of treatment for early disease and results can be improved by adding a structural graft such as vascularised fibula or a trabecular metal implant. Proximal femoral osteotomy can be used successfully in higher stage disease with a small amount of femoral head involvement, although generalised osteopenia may delay or prevent healing of the osteotomy. Trap-door grafting can restore the sphericity of the femoral head and...
Results of total hip replacements in renal transplant patients

Table I summarises the results of the current studies of THR in renal transplant patients. Comparison is difficult as there are few studies, the numbers of patients are small and follow-up is generally short, although a recent report by Goffin, Baertz and Rombouts reports 20-year follow-up results in their patient series. Authors often study primary and revision THRs together to increase numbers available for review. The arthroplasties are often carried out by numerous surgeons, each with individual preferences, and the scoring systems for post-operative assessment, if included, vary from author to author. First-generation cementing techniques are combined with current techniques, and no constant implant is used, except in the study of femoral & acetabular components at 20 yrs/1.2 & 36.2 at 10 & 20 yrs

Table I. Results for total hip replacements in renal transplant patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age at arthroplasty (yrs)</th>
<th>Number of arthroplasties (technique)</th>
<th>Mean follow-up</th>
<th>Results (Mean Harris pre-operative/post-operative hip scores)</th>
<th>Rate of revision/loosening (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenzora and Sledge et al</td>
<td>37</td>
<td>27 (cemented)</td>
<td>23 mths</td>
<td>45/100</td>
<td>0/0</td>
</tr>
<tr>
<td>Bradford et al</td>
<td>32</td>
<td>60 (cemented)</td>
<td>41 mths</td>
<td>38/97</td>
<td>2/2</td>
</tr>
<tr>
<td>Devlin et al</td>
<td>36</td>
<td>53 (cemented)</td>
<td>86 mths</td>
<td>NA/80% (good to excellent)</td>
<td>NA/25</td>
</tr>
<tr>
<td>Stauffer and Segal et al</td>
<td>37.4</td>
<td>16 (cemented)</td>
<td>24 mths</td>
<td>NA/44% (good to excellent)</td>
<td>NA/0</td>
</tr>
<tr>
<td>Radford et al</td>
<td>49</td>
<td>24 (cemented)</td>
<td>72 mths</td>
<td>17/86</td>
<td>NA/17</td>
</tr>
<tr>
<td>Cheng et al</td>
<td>33</td>
<td>76 (cemented)</td>
<td>10 yrs (minimum)</td>
<td>NA/88</td>
<td>9 at 5 yrs, 22 at 10 yrs, 40 overall/NA</td>
</tr>
<tr>
<td>Deo et al</td>
<td>40.9</td>
<td>34</td>
<td>5.2 yrs</td>
<td>24/89</td>
<td>31/46 for cemented, 19/0 for bipolar, 0/0 for cementless</td>
</tr>
<tr>
<td>Murzic and McCollum et al</td>
<td>36</td>
<td>32 (32 cemented, 13 cementless)</td>
<td>6.4 yrs</td>
<td>24/89</td>
<td>31/46 for cemented, 19/0 for bipolar, 0/0 for cementless</td>
</tr>
<tr>
<td>Alpert et al</td>
<td>39</td>
<td>27 (cementless)</td>
<td>48 mths</td>
<td>36/88</td>
<td>NA/0</td>
</tr>
<tr>
<td>Grevitt and Spencer et al</td>
<td>40</td>
<td>22 (bipolar uncemented)</td>
<td>40 mths</td>
<td>27/88</td>
<td>4.5/4.5</td>
</tr>
<tr>
<td>Orwin et al</td>
<td>34.6</td>
<td>16 (bipolar uncemented)</td>
<td>40 mths</td>
<td>31/94.2</td>
<td>33 subsidence, no progression</td>
</tr>
<tr>
<td>Shrader et al</td>
<td>46</td>
<td>36 (cemented)</td>
<td>11 yrs</td>
<td>61/85 (81% good to excellent)</td>
<td>36/33</td>
</tr>
<tr>
<td>Goffin et al</td>
<td>38</td>
<td>93 (cemented)</td>
<td>216 mths</td>
<td>NA</td>
<td>0 at 10 yrs, 21.2 &amp; 33.4 for femoral &amp; acetabular components at 20 yrs/1.2 &amp; 36.2 at 10 &amp; 20 yrs</td>
</tr>
</tbody>
</table>

* NA, not available
† references 2 and 35 include an overlap of patients. The former is the most recent report that includes added patient data as well as further follow-up of patients of the latter study

give good to excellent results in higher stage disease but at the expense of more extensive surgery. Hip resurfacing arthroplasty has been used extensively in Europe, with current metal-on-metal implants providing good functional outcomes in high-staged disease with minimal complications, although long-term results are not yet available.

Results of total hip replacement in renal transplant patients

The age at THR for renal transplant patients with AVN of the femoral head is approximately 38 years (16 to 70). Patients develop symptoms at a mean of 20.5 months (3 to 132) and require THR at a mean of 35 months (2 to 175) after transplant. These patients are at greater risk of major morbidity than their non-transplant counterparts.

Thorough pre-operative planning is imperative for renal transplant patients. They are often anaemic and may benefit from erythropoietin treatment (40 000 units subcutaneously on days 21, 14 and 7 pre-operatively, and on the day of surgery), or pre-operative autologous blood donation. Coordination with the transplant team is required; they can help optimise the medical management of patients. Modern immunosuppressant regimens are complex and need to be carefully manipulated peri-operatively.

Table I summarises the results of the current studies of THR in renal transplant patients. Comparison is difficult as there are few studies, the numbers of patients are small and follow-up is generally short, although a recent report by Goffin, Baertz and Rombouts reports 20-year follow-up results in their patient series. Authors often study primary and revision THRs together to increase numbers available for review. The arthroplasties are often carried out by numerous surgeons, each with individual preferences, and the scoring systems for post-operative assessment, if included, vary from author to author. First-generation cementing techniques are combined with current techniques, and no constant implant is used, except in the study by Goffin et al. This lack of uniformity can skew results, especially with regard to complications. Therefore, reports may be misleading. Nevertheless, useful information can be gained. Woods et al published the first report of successful THR in a renal transplant patient who had bilateral AVN of the femoral head treated with cemented Charnley implants and without complications at 26 months follow-up. Kenzora and Sledge published the first case series of THR in renal transplant patients. They found the Harris hip scores improved from a mean of 45 to 100 post-operatively, without infection or aseptic loosening, up to 23 months after operation.
Bradford et al, however, first reported that renal transplant patients can have extensive complications after THR, despite excellent pain relief and outcome scores. Karas et al reported a significant complication rate and concluded that alternatives to THR should be sought in these patients. Despite adequate pain relief in their patients, Devlin et al made similar conclusions.

Most authors, however, have reported encouraging results with THR in renal transplant patients. With a minimum of ten years follow-up, they observed that 78% of prostheses survived and good outcome scores were maintained with minimal complications. They concluded these results were analogous to those in older patients with osteoarthritis rather than those in young non-transplant patients. Shrader et al reported 81% good to excellent results despite rates of loosening and revision of 36% and 33% respectively. Goffin et al considered the diminished life expectancy in these patients warranted THR as early as possible. Deo et al recommended THR as long as the surgeon was prepared for a high complication rate. If there is no acetabular erosion, Grevitt and Spencer found that bipolar hemiarthroplasty was also a good option.

Cheng et al reported the first long-term follow-up study of THR in renal transplant patients. With a minimum of ten years follow-up, they observed that 78% of prostheses survived and good outcome scores were maintained with minimal complications. They concluded these results were analogous to those in older patients with osteoarthritis rather than those in young non-transplant patients. Shrader et al reported 81% good to excellent results despite rates of loosening and revision of 36% and 33% respectively. Goffin et al reported that 100% of cemented Charnley THRs survived without loosening at a mean of ten years, with the survival rate dropping to 63.8% at 20 years and concluded that, at least for the first ten years, cemented THRs in renal transplant patients behave like age-matched controls.

It was originally thought that cementing was the only viable method of fixation in renal transplant patients because of poor bone stock. More recent evidence suggests that press-fit prostheses have similar survivorship. Post-operative pain relief is excellent, though long-term results for press-fit prostheses are lacking. Cementless THR or bipolar arthroplasties are not contraindicated in renal transplant patients unless a patient is dialysis-dependent after a failed transplant.

Complications. The infection rate of THRs in renal transplant patients varies between studies. Many report no increased risk. Others report infection rates between 1.3% and 19%. but Deo et al reported a single case of infection which occurred 3.5 years after THR, while Karas et al reported a 6% infection rate, all secondary to haematogenous seeding. The major concerns regarding infection relate to fatal deep-seated sepsis. Bradford and Murzic each reported a case of fatal sepsis following deep infection. Bradford et al’s patient had received many transplants, was on chronic haemodialysis, and underwent cholecystectomy for acute cholecystitis one month prior to THR. It was recognised that surgery should have been delayed. Tannenbaum et al found a very high infection rate after THR in patients who had received a renal or liver transplant, and patients taking cyclosporine A had a 33% increased risk for infection. They recommended diligent investigation of patients with a stable arthroplasty who presented with pain. They suggested broad-spectrum antibiotics pre- and post-operatively, antibiotic cement for implantation and diligent antibiotic prophylaxis for dental and urinary procedures.

Although infection rates in all studies vary widely, the majority of authors do not consider infection rates in renal transplant patients to be significantly greater than in non-transplant patients. Nevertheless the wide variance makes it difficult to establish a consensus. From available data, it appears that the fear of increased risk of early or late infection is unjustified in these patients despite chronic immunosuppression.

Thromboembolic events are higher in renal transplant than non-transplant patients. In the studies which cover such events, the rates ranged between 1.8% and 9%. In a limited number of patients, the rate of non-fatal pulmonary embolism was between 1.8% and 3%. Devlin et al reported one acute post-operative fatality. Although one reason for the higher number of thromboembolic events may be the small number of patients, a more likely reason is that these patients are at greater risk for thrombus because of their poor general health. There is wariness in anti-coagulating renal transplant patients on corticosteroids because of the risk of bleeding from a peptic ulcer. These patients therefore may not receive appropriate thromboprophylaxis. Routine prophylaxis with newer anticoagulants such as enoxaparin and fondaparinux should be used, along with appropriate ulcer prophylaxis with a histamine receptor 2 blocker or proton pump inhibitor.

Though mortality rates are high in renal transplant patients, mortality is caused by medical co-morbidities rather than the underlying THR. Mortality rates at 15 years are as high as 42% though with newer immunosuppression regimes, this is decreasing. Given such high mortality at a young age, some authors recommend that THR in symptomatic patients be carried out early in order to give them the longest possible pain relief.

Heterotopic ossification is a common complication of THR in renal transplant patients. In most, the condition is asymptomatic and rarely requires treatment. Rates range between 19% and 80% and are generally Brooker class I or II. It is thought that renal transplant patients are more susceptible to heterotopic bone formation because of altered calcium metabolism. Post-operative haematoma, transient sciatic nerve palsy, trochanteric non-union, and peri-prosthetic fracture have all been reported, but are rare. Despite relative osteopenia peri-prosthetic fractures are unusual.

The rate of dislocation for THR in renal transplant patients ranges between 0% and 16.7%. Bradford et al reported the highest number of dislocations, with a rate almost eight times higher than that of non-transplant patients. Many of the studies were from the time when capsular repair after a posterolateral approach was uncommon. Other possible reasons for dislocation...
include accidents, overaggressive physiotherapy and generalised soft-tissue laxity. Alpert et al.16 suggest that soft-tissue healing is delayed in renal transplant patients because of chronic steroid use. General hip precautions should be diligently maintained, especially in the early post-operative period and if a posterolateral surgical approach is chosen.

It has been suggested that renal transplant patients with THR have a greater risk for aseptic loosening because of altered calcium metabolism. Early studies in these patients found no problems with loosening, but follow-up was short.32,34 Early loosening rates were thought to be less than 5%,5,33 but long-term studies suggest otherwise, with loosening rates ranging between 13% and 46% within five to ten years.2,7,8,29,32,35,37 Proposed hypotheses for these high rates of loosening include younger age, increased activity levels, hip bilaterality, pre-transplant renal osteodystrophy, steroid-induced AVN of the femoral head and hyperparathyroidism secondary to chronic steroid use.8,13,37 Devlin et al.9 concluded that this latter combination suppresses bone formation and increases resorption, particularly at the bone-cement interface, thus making it the prime factor for mechanical loosening in renal transplant patients. First-generation cementing techniques were widely used in most studies, which alone can increase the risk for early loosening.2,7,9,32,33,40 Pulsed-steroid doses or chronic steroid use have not been found to significantly alter bone in growth around cementless implants.36

Despite successful transplantation, renal allograft recipients require ongoing measures to prevent metabolic bone disease. Underlying bone stock can be affected not only by glucocorticoid-use, but also as a result of renal osteodystrophy. The rate of bone loss is greatest in the first post-operative year and then gradually tapers off at approximately ten years after transplantation.44,45 Steroid therapy is a major cause of bone loss, especially in the first year post-transplant when doses for maintenance immunosuppression are optimised and large pulsatile doses are required to prevent rejection.46 The use of all newer immunosuppressants, except for mycophenolate, potentiates underlying glucocorticoid-induced osteoporosis in renal transplant patients.44 Post-transplantation renal osteodystrophy is characterised by increased bone resorption and decreased bone formation.47 This is secondary to diminished parathyroid hormone (PTH) levels after transplantation, as well as accompanying steroid use which further decreases osteoblast activity.48 Conversely, between 25% and 50% of renal transplant recipients continue to have elevated levels of PTH one and two years after transplantation, respectively, and this can maintain a state of secondary hyperparathyroidism.44 The longer a patient is on haemodialysis before transplantation, the greater is the reduction of bone stock, and this loss of bone stock continues even after successful transplantation.49

Although there are some drugs approved and in use in maintaining bone density in renal transplant recipients, such as vitamin-D analogues, bisphosphonate therapy has shown promise in not only maintaining but also increasing bone stock in these patients.49 Bone mineral density in glucocorticoid-induced osteoporosis is increased significantly with the use of oral alendronate.50 Other studies have shown that bisphosphonates significantly increased bone mineral density in the immediate post-operative period in renal transplant patients who have undergone THR.47,49 Archimotlagh, Rittmeister and Hennigs51 found that oral alendronate in the first six months after THR significantly diminished peri-prosthetic bone loss. Overall, it may be reasonable to infer that bisphosphonates may increase bone mineral density and diminish peri-prosthetic bone loss in these patients. As the rise of aseptic loosening with subsequent revision is markedly increased in renal transplant patients, it may be beneficial to give post-operative bisphosphonate therapy not only to maintain but also improve, peri-prosthetic bone stock, and potentially to increase the survival of implants.

A warning is required concerning universal bisphophonate use in renal transplant patients. They may have a low-turnover secondary hyperparathyroidism which may reduce bone density. This can occur particularly with prolonged and intensive use of these agents.46 If suspected, a tetracycline-labelled bone biopsy can be used to rule out an underlying dynamic condition of bone prior to starting treatment.47 The effective duration and dose of bisphosphonate administration has yet to be determined.

The rate of complications in renal transplant patients undergoing THRs can be reduced. Pre-operatively, anaemia should be effectively controlled. Peri-operatively, broad-spectrum antibiotic cover is recommended, and generalised hip precautions should be followed. Thromboprophylaxis should be administered concomitantly with appropriate prophylaxis for peptic ulceration, and diligent follow-up by the patient’s nephrologist or transplant co-ordinator is essential. Bone metabolism should be managed appropriately and the orthopaedic surgeon should follow these patients carefully. Follow-up should be closer in the first year with subsequent yearly visits for the first four years and every other year thereafter.39 As recommended by Tannenbaum et al.,6 any new onset of renal transplant pain in a patient with a stable THR should be investigated aggressively to exclude septic arthritis.

References