

# Calcineurin Inhibitors and Post-Transplant Hyperlipidaemias

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## Abstract

Cardiovascular disease is now the leading cause of death in transplant recipients. This is due, in part, to the vulnerability of these patients to a complicated set of conditions including hypertension, diabetes mellitus, and post-transplant hyperlipidaemia (PTHL). PTHL is characterised by persistent elevations in total serum cholesterol, low density lipoprotein cholesterol and triglyceride levels.

The causes of PTHL are complex and not fully understood, however several classes of immunosuppressants including the corticosteroids, rapamycins and calcineurin inhibitors, appear to play a role. PTHL has been observed in most studies in which patients received calcineurin inhibitor-based regimens, and has been observed with both tacrolimus and cyclosporin. Comparing these calcineurin inhibitors with regard to the relative incidence or severity of PTHL occurring during treatment is difficult because of the use of higher doses of corticosteroids

in cyclosporin-based regimens, as compared with tacrolimus-based regimens. However, current expert opinion suggests that the discrepancies in the relative incidence and severity of PTHL are largely accounted for by this difference in corticosteroid dose. At this point in time, evidence for potential differences is scant and inconclusive. Further study is needed, not only to investigate differences in lipid profile, but also of the relative effects of these immunosuppressants on long term graft function as well as on cardiovascular morbidity and mortality.

PTHL can be successfully managed with a combination of dietary management, reduction and, if appropriate, withdrawal of corticosteroids, and the administration of lipid-lowering drugs. With this combination of therapeutic options, the threats to long term health posed by PTHL may be effectively addressed.

The prevention of cardiovascular disease has become a major challenge for transplantation medicine in the new century. Now the leading cause of death, it accounts for more than 50% of all mortality in renal transplant recipients.<sup>[1]</sup>

The prevalence of ischemic heart disease is 6.4 times higher in transplant recipients without diabetes mellitus than in the age-adjusted general population, and in transplant recipients with diabetes mellitus, the prevalence is even higher – 20.8 times.<sup>[2]</sup> Major contributors to this increased risk include hypertension, diabetes mellitus, and post-transplant hyperlipidaemia (PTHL).<sup>[3-6]</sup> All of these diseases may have an impact on patient mortality and graft loss. Moreover, they appear to be caused to varying degrees by the immunosuppressive agents used to prevent acute rejection. Agents include corticosteroids, sirolimus, and the calcineurin inhibitors, tacrolimus and cyclosporin. This review will focus on the role of the calcineurin inhibitors in PTHL and on the complex relationship linking immunosuppression, hyperlipidaemia, and cardiovascular disease.

## 1. Clinical Profile of Post-Transplant Hyperlipidaemia (PTHL)

The most prominent feature of PTHL is an elevation in total cholesterol, which increases in a dose-dependent fashion with several classes of immunosuppressants.<sup>[4-10]</sup> Most of this increase is the result of elevation of low density lipoprotein-cholesterol (LDL-C) levels. Very low density lipoprotein-cholesterol (VLDL-C) levels are frequently

increased, and increases in triglyceride levels are also common.<sup>[2,8-10]</sup> By contrast, high density lipoprotein-cholesterol (HDL-C) levels vary.<sup>[2,10,11]</sup> Other features of PTHL include increased levels of apolipoprotein B and lipoprotein(a).<sup>[4]</sup> Additionally, increased LDL oxidation may occur.

Threshold values commonly used in reporting hyperlipidaemia are 240 mg/dl for total serum cholesterol, 130mg for LDL-C, 200 mg/dl for triglycerides and 30 mg/dl for lipoprotein(a).<sup>[12]</sup> The clinical profile in individual patients may vary, but any patient in whom just 1 lipid parameter exceeds its threshold can be said to have PTHL.

PTHL typically develops 3 to 6 months after transplantation. Following an initial steep rise in lipid levels, there may be slight improvement. In general, the levels then stabilise and remain elevated at 12 months post transplantation.<sup>[13]</sup> In the longer term, it is not yet clear whether lipid levels return further towards baseline, or whether such reductions simply reflect gradual reductions in the doses of immunosuppressants used over time.

### 1.1 Incidence and Prevalence

Estimates of the overall incidence of PTHL vary widely, from 22 to 54%, with estimates varying according to graft type, although some of this variation has been attributed to lack of standardisation in the reporting of lipid levels.<sup>[5]</sup> PTHL is, however, well documented and has been observed regardless of the type of organ received.

In kidney- and liver-graft-recipients, the prevalence of PTHL has been estimated at 40 to 50%.<sup>[14]</sup>

In a study by Jindal and colleagues,<sup>[15]</sup> 58% of liver transplant recipients had evidence of hyperlipidaemia (importantly with respect to cardiovascular risk, 37% of patients also had diabetes mellitus). In a study by Kasiske,<sup>[16]</sup> total serum cholesterol was greater than 240 mg/dl in as many as 63% of renal graft recipients with 60% having LDL-C levels greater than 130 mg/dl. Triglyceride levels were greater than 200 mg/dl in 36% of patients in this study, and lipoprotein(a) levels were greater than 30 mg/dl in 23% of recipients. Pancreatic transplantation appears to be associated with a less abnormal lipid profile, and combined kidney/pancreas transplants are associated with a lower incidence of PTHL in recipients than in patients who received kidney transplantation alone.<sup>[17]</sup> However, in heart transplant recipients, the prevalence of hyperlipidaemia may be as high as 80%. Even after dietary modification, Ballantyne and colleagues<sup>[18]</sup> noted LDL-C levels greater than 130 mg/dl in 64% of patients and triglyceride levels of 200 mg/dl or greater in 41%.

## 2. Impact of PTHL

Major trials in the general population have shown the impact of hyperlipidaemia on cardiovascular disease and mortality, and have demonstrated the benefits of lowering lipid levels even in patients with normal cholesterol levels.<sup>[19-21]</sup> Although less well studied in transplant recipients, a similar impact would be expected. Consistent with this expectation is a study by Valantine and colleagues,<sup>[22]</sup> in which they showed that high lipid levels predicted mortality and post-transplant coronary artery disease in patients with heart transplants. In another study, a 4 year prospective randomised trial, heart transplant recipients taking simvastatin had both an improved long term survival (88.6 vs 70.3%,  $p = 0.05$ ) and a decreased incidence of accelerated graft disease (16.6 vs 42.3%,  $p = 0.045$ ).<sup>[23]</sup>

### 2.1 Impact of Hyperlipidaemia on Cardiovascular Disease

It is generally accepted that PTHL contributes significantly to the increased cardiovascular dis-

ease burden in transplant patients even though the exact relationship between PTHL and cardiovascular disease is not fully elucidated in this population. For example, in renal transplant recipients, Aakhus and colleagues<sup>[24]</sup> found total serum cholesterol levels to be a predictor of ischaemic heart disease but not of cerebrovascular or peripheral vascular disease. In another multivariate analysis in renal graft recipients, Kasiske<sup>[25]</sup> similarly found that total cholesterol (although not HDL-C or triglyceride) levels were an independent risk factor for both ischaemic heart disease and all vascular disease, but not for cerebrovascular disease. In a later study, Kasiske and colleagues found that HDL-C (but not total or LDL-C) levels predicted ischaemic heart disease.<sup>[26]</sup> A third study, again by Kasiske and colleagues,<sup>[27]</sup> found that HDL-C and total cholesterol levels independently predicted ischaemic heart disease. There is still a need for further investigation.

### 2.2 Impact of Hyperlipidaemia on Chronic Rejection

In addition to contributing to cardiovascular disease in transplant recipients, hyperlipidaemia might also contribute to the development of chronic allograft rejection. Worsening arteriosclerosis, intimal thickening, and vascular luminal obliteration, which have been described as characteristic of chronic rejection, are also associated with hyperlipidaemia.<sup>[28]</sup> *In vitro* studies have shown that oxidised LDL has effects on endothelial cells, smooth muscle cells, monocytes, and macrophages, which could contribute to chronic rejection and accelerated arteriosclerosis. LDL-C, particularly when oxidised, also has been shown to stimulate the synthesis of cytokines, growth factors, and extracellular matrix proteins in renal glomerular mesangial cells.<sup>[29]</sup> Finally, on a clinical level, LDL oxidation has been shown to be increased in transplant recipients. Whether this translates into increased rates of chronic rejection and graft loss remains to be proven.<sup>[30-32]</sup>

In recipients of heart transplants, which are particularly prone to vasculopathy, McManus and col-

leagues<sup>[33]</sup> reported greater lipid accumulation within the coronary arteries of heart graft recipients compared with age-matched control individuals. In another study, Valantine<sup>[34]</sup> reported that increasing intimal thickness correlated directly with blood lipid levels.

Some studies in renal transplant patients have also indicated that hyperlipidaemia is a risk factor for chronic rejection. With respect to graft survival, 4 studies<sup>[26,34-36]</sup> in renal transplant recipients demonstrated no impact of hypercholesterolaemia, possibly because appropriate therapy (e.g. with lipid-lowering agents) prevented cardiovascular complications. However, a study in younger patients showed that hypercholesterolaemia was linked to early graft failure<sup>[37]</sup> and another study of in male transplant recipients linked chronic rejection with hypercholesterolaemia.<sup>[38]</sup> A further study showed LDL-C to be a predictor of renal graft outcome; graft outcome was dependent on the level of LDL-C.<sup>[39]</sup> Moreover, a study by Divakar and colleagues<sup>[9]</sup> showed lower LDL and increased HDL-C levels to be independent correlates of improved kidney graft survival.

Elevated total and LDL-C and reduced HDL-C are probably all valid independent predictors of adverse outcomes in transplant recipients. Furthermore, elevated triglycerides are probably associated with an adverse outcome as well.

### 3. Aetiology of PTHL

The aetiology of PTHL is complex. Known risk factors for high total cholesterol and LDL-C following transplantation include obesity, male gender, and Black race.<sup>[40,41]</sup> The incidence of obesity, a problem to which corticosteroids contribute, is higher in transplant patients than in the general population. Diet is a significant contributor to the atherosclerotic process in the general population<sup>[42]</sup> and is probably of equal importance in transplant patients.

Genetic variations may contribute to PTHL. Increased HDL levels have been associated with certain polymorphisms of the apolipoprotein A-I gene,<sup>[43]</sup> and increased triglyceride levels have

been observed in patients with an E2 allele as compared with other genotypes of apolipoprotein E.<sup>[44]</sup> Renal insufficiency and overt proteinuria may also contribute to PTHL as may certain antihypertensive agents, e.g.  $\beta$ -adrenoceptor antagonists and diuretics. In addition, several classes of immunosuppressants, the subject of this review, play a causative role.

#### 3.1 Immunosuppressants

The immunosuppressants most associated with PTHL are corticosteroids, calcineurin inhibitors, and rapamycins. Although the association between these agents and hyperlipidaemia has been shown both clinically and in experimental models, the molecular mechanisms by which they cause PTHL are still uncertain.

##### 3.1.1 Corticosteroids

The major contributing role of corticosteroids in PTHL has been well documented. Corticosteroids promote insulin resistance, causing secondary hyperinsulinaemia, with a reduction in lipoprotein lipase activity, overproduction of triglycerides, and secretion of VLDL-C.<sup>[26,45]</sup> Clinical studies have demonstrated a positive relationship between corticosteroid dose and hyperlipidaemia in renal transplant patients,<sup>[46-48]</sup> and in liver graft recipients.<sup>[15]</sup> Similarly, total serum cholesterol levels have been shown to be higher in renal transplant patients treated with cyclosporin and prednisone compared with patients treated with cyclosporin and mycophenolate mofetil.<sup>[49]</sup> Interestingly, HDL-C levels may be increased by corticosteroids, which may account in part for the variability in HDL-C levels observed in transplant patients.<sup>[50]</sup>

##### 3.1.2 Calcineurin Inhibitors

It is generally accepted that calcineurin inhibitor therapy (cyclosporin and tacrolimus) is associated with hyperlipidaemia. Postulated mechanisms include inhibition of bile acid synthesis and binding of the drug to the LDL receptor with reduction of its activity.<sup>[14]</sup> Neither mechanism is well established and other mechanisms, including a decrease in lipoprotein lipase activity and impairment of

LDL catabolism, may be involved.<sup>[51]</sup> Calcineurin inhibitors additionally may increase the susceptibility of LDL to oxidation and may increase plasma homocysteine levels.<sup>[4]</sup> Transplant patients with a history of ischaemic heart disease have also been found to have reduced levels of antibodies against oxidised LDL, a reduction that correlates with the level of immunosuppression.<sup>[52]</sup>

For tacrolimus, the incidence and severity of PTHL is perceived within the transplant community as less than that seen with cyclosporin. However, differences in the doses of corticosteroids given to cyclosporin- and tacrolimus-treated patients prevent an objective comparison as does the lack of long term clinical data in transplant patients receiving tacrolimus. Cyclosporin has been more extensively studied and much of the understanding about the role of calcineurin inhibitors in PTHL and cardiovascular morbidities has evolved from studies of cyclosporin. An additional complicating factor is that the database for cyclosporin is largely based on an older formulation of cyclosporin (Sandimmune®<sup>1</sup>), which was replaced by a microemulsion formulation (Neoral®) because of its more consistent absorption. The impact of the formulation change on PTHL is unknown, but differences in excipients may possibly result in selective metabolic differences such as nitric oxidation.

Studies with cyclosporin monotherapy have confirmed the hyperlipidaemic effects of the calcineurin inhibitors.<sup>[2,53-55]</sup> However, the addition of corticosteroids to cyclosporin therapy appears to account for much of the problem of hyperlipidaemia seen in clinical practice. In renal transplant patients, Locsey and colleagues<sup>[56]</sup> reported PTHL in only 3 of 17 patients given cyclosporin monotherapy, compared with 30 of 55 patients treated with combination cyclosporin/corticosteroid therapy. Similarly, in a parallel group study in kidney transplant recipients, Hricik and colleagues<sup>[57]</sup> found that discontinuation of corticosteroids reduced total cholesterol levels by over 1 mmol/L in cyclosporin-treated patients.

### **3.1.3 Other Fungal-Derived Immunophilin-Binding Macrolides**

Like the calcineurin inhibitors, rapamycins are fungal-derived immunophilin-binding macrolides. However they have a different mode of action within the cell. The rapamycins have been associated with even greater hyperlipidaemia than cyclosporin, producing significantly higher total cholesterol and triglyceride levels.<sup>[58,59]</sup>

In an open-label European multicentre study, the incidence of hypercholesterolaemia was 44% and the incidence of hypertriglyceridaemia was 51% in patients who received sirolimus, compared with 14 and 12% respectively in the cyclosporin arm.<sup>[60]</sup> In a separate US trial, patients who received sirolimus 2 or 5mg/day along with cyclosporin and prednisone experienced hypercholesterolaemia rates of 33 and 37%, and hyperlipidaemia rates of 34 and 42% at 12 months.<sup>[61]</sup>

A phase I study of everolimus evaluated the effects of 0.75, 2.5, and 7.5 mg/day of everolimus when given in combination with cyclosporin and prednisone. Patients receiving everolimus 0.75 mg/day had similarly increased levels of total serum cholesterol and triglycerides.<sup>[62]</sup> However the patient groups receiving everolimus 2.5 and 7.5 mg/day had increases of 89.5 and 54.9% respectively in serum cholesterol, and 459 and 159% respectively in triglycerides.

### **3.2 Direct Effects of Immunosuppressants on Atherosclerosis**

In addition to contributing to PTHL, immunosuppressants may also directly affect the development of atherosclerosis. Although immune cells present in atherosclerotic plaques have been thought to contribute to atherogenesis, there is emerging evidence that both cellular and humoral immune responses may actually protect against atherogenesis, an effect that immunosuppression may attenuate. In class I major histocompatibility complex (MHC)-deficient mice for example, atherosclerosis develops at an accelerated rate.<sup>[63]</sup> In rabbits, immunisation against oxidised or native LDL has been shown to decrease atherosclerosis.<sup>[64]</sup> There-

**1** Use of tradenames is for product identification purposes only and does not imply endorsement.

fore, reduced immunologic function may contribute to cardiovascular disease independent of the major metabolic and rheological risk factors associated with immunosuppressive therapy.

#### **4. PTHL and the Calcineurin Inhibitors: Clinical Studies**

A large number of studies have compared the relative effects of cyclosporin and tacrolimus on lipid profiles in transplant recipients. However, the use of higher doses of corticosteroids in the majority of cyclosporin studies introduced a bias. Results of several such studies in patients with renal and kidney grafts will be discussed. Although not discussed here, similar results have been obtained in heart transplant recipients, including children.

##### **4.1 Renal Transplantation**

Hohage and colleagues<sup>[65]</sup> investigated the comparative effects of tacrolimus and cyclosporin in kidney transplant patients. After a median of 6 months post-transplant, there were no significant differences in levels of total cholesterol, triglycerides, or HDL-C between the cyclosporin and tacrolimus groups. Mean LDL-C, lipoprotein(a), and fibrinogen levels were lower in the tacrolimus group, however the corticosteroid dosage was 11.0 mg/day in the tacrolimus group compared with 19.0 mg/day in the cyclosporin group. Vela and colleagues<sup>[66]</sup> reported that tacrolimus prevented the increase in total cholesterol and apolipoprotein B levels seen in renal transplant patients with cyclosporin, but noted that this also could have been a result of the use of lower dosages of corticosteroids in patients receiving tacrolimus. In the major US trial comparing tacrolimus with the Sandimmune® formulation of cyclosporin, hypercholesterolaemia was more common in the cyclosporin group, but again corticosteroid use was greater.<sup>[67]</sup> By contrast, in a smaller study evaluating the Neoral® formulation, elevations in total serum cholesterol as well as LDL-C were not as great at 6 months in patients treated with tacrolimus compared with those treated with cyclosporin.<sup>[68]</sup> This was despite the fact that all patients received a similar cortico-

steroid regimen post-transplant (including a maintenance dosage of 10 mg/day prednisone). Interestingly, the authors of this study also noted that there was no significant difference in cardiovascular deaths between treatment groups at 1 year. However, they stated that 1 year follow-up may not be long enough to assess the long term risks of the differences in lipid levels.

##### **4.2 Liver Transplantation**

An objective comparison of the effects of cyclosporin and tacrolimus on the lipid profile in liver transplant patients is similarly difficult because of differences in corticosteroid dose. In a study of lipid metabolism 2 years after transplantation, levels of total serum cholesterol or triglycerides did not significantly differ between treatment groups although LDL-C and apolipoprotein B levels were significantly greater in patients receiving cyclosporin compared with tacrolimus.<sup>[69]</sup> The mean dosages of corticosteroids in this study were 5.77 mg/day in the cyclosporin group and 4.66 mg/day in the tacrolimus group. Likewise, in a major US trial comparing tacrolimus with the Sandimmune® formulation of cyclosporin, total serum and LDL-C levels were higher at 6 months and 1 year in the cyclosporin group.<sup>[70]</sup> The authors noted that the difference in corticosteroid dose could account for some or all of the observed differences in lipid profiles. In the equivalent European trial, similar lipoprotein metabolism results were obtained from substudies of the population.<sup>[71]</sup>

In a small study in liver transplant recipients who were matched for corticosteroid dose, there were no significant differences between groups at 1 year post-transplant in levels of total cholesterol, triglycerides, LDL-C or HDL-C.<sup>[71]</sup> In another study, gender-specific differences in lipid profile were observed even after corticosteroid withdrawal. However, the number of patients not taking corticosteroids was small, and cholesterol and triglyceride level elevations not exceeding hyperlipidaemia threshold values occurred with both cyclosporin and tacrolimus treatment.<sup>[72]</sup> Finally, results of another small study by Fernandez-

Miranda<sup>[73]</sup> determined corticosteroid therapy to be the major determinant of increased cholesterol levels, as did a 4-year long term study by Charco and colleagues,<sup>[74]</sup> which showed that cholesterol levels were similar in patients treated with cyclosporin or tacrolimus once corticosteroids were stopped.

#### 4.3 Conversion Studies

Switching from cyclosporin to tacrolimus therapy has been reported to reduce levels of total cholesterol by 10 to 15%, and LDL-C by 20 to 25%. McCune and colleagues,<sup>[75]</sup> for example, reported a 23% reduction of LDL-C levels in kidney graft recipients who were switched from cyclosporin to tacrolimus. However, in many of these studies, there was also a concomitant reduction in corticosteroid dose. Furthermore, some trials have failed to show any improvement in cholesterol levels.<sup>[76]</sup> Pratschke and colleagues<sup>[76]</sup> found no reduction in total serum cholesterol levels after 1 year despite a switch to tacrolimus. Although triglycerides fell from 212 to 172 mg/dl the number of patients receiving corticosteroids also decreased, which may have impacted the improvement in triglyceride levels.

### 5. Treatment of PTHL

There is still some lack of consensus as to the threshold for intervention with lipid-lowering agents in the transplant population and whether to follow the same guidelines as those used for the general population. Factors to be considered include age, gender, the presence of other cardiovascular risk factors, past history of cardiovascular disease, and costs of intervention. However, regardless of the threshold that is chosen for intervention, pharmacological therapy must be accompanied by diet and lifestyle modification. An additional consideration in transplant patients is the possible interaction of immunosuppressants with drugs used to lower serum lipids.

#### 5.1 Diet and Lifestyle Intervention

All transplant recipients should be encouraged to control bodyweight and reduce the intake of unsaturated fat and cholesterol. Regular exercise and nonsmoking should also be encouraged. Diets rich in fish oils<sup>[77]</sup> containing omega-3 fatty acids have been reported to improve renal haemodynamics and serum lipid levels,<sup>[5]</sup> decrease production of interleukin-1 and tumour necrosis factor,<sup>[78]</sup> and reduce post-transplant hypertension and chronic rejection. Soya protein has also been reported to reduce serum cholesterol levels.<sup>[79]</sup> However, these findings need to be confirmed in larger, multi-centre studies.

#### 5.2 Lipid-Lowering Agents in the Management of PTHL

Several lipid-lowering agents are available, but not all are appropriate for use in transplant recipients. Cholestyramine, for instance, may interfere with cyclosporin absorption, and nicotinic acid (niacin) may cause glucose intolerance, hyperuricaemia, and hepatotoxicity, as well as flushing.<sup>[5]</sup> Fibrin acid derivatives, such as gemfibrozil, have been shown to improve the LDL/HDL ratio in renal transplant patients and may have a role in recipients with hypertriglyceridaemia. However, they may not be suitable for use in liver graft recipients because of the potential to increase the incidence of gallstones.<sup>[80]</sup>

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors, more commonly known as statins, have been widely and successfully used to treat PTHL. The major HMG CoA reductase inhibitors (table I) are effective in lowering LDL-C levels and also have good safety profiles. However, competition between certain HMG CoA reductase inhibitors (atorvastatin, cerivastatin, lovastatin, and simvastatin) and calcineurin inhibitors for the same hepatic metabolising enzymes (these HMG CoA reductase inhibitors are predominantly metabolised by the cytochrome P450 3A4 isoenzyme) can increase blood concentrations of the calcineurin inhibitors.<sup>[81]</sup> Fluvastatin has several meta-

bolic pathways available<sup>[82]</sup> and pravastatin is not significantly metabolised by this enzyme. Therefore, fluvastatin and pravastatin are considered to be the HMG CoA reductase inhibitors of choice in patients receiving calcineurin inhibitors.

In studies in renal transplant recipients, fluvastatin has been shown to reduce levels of total cholesterol by 13 to 27%, LDL-C by 22 to 38%, and apolipoprotein B by 13%.<sup>[82-84]</sup> Similarly, in a combined study of cardiac and renal transplant recipients, Schrama and colleagues<sup>[83]</sup> found that fluvastatin 20 to 40 mg/day reduced levels of total serum cholesterol by 20%, LDL-C by 30% and HDL2-C by 35% without causing any subclinical muscle pathology.

Pravastatin has also been shown to effectively reduce total or total and LDL-C in patients with renal or heart transplants<sup>[85-87]</sup> without adversely affecting graft function or creatinine kinase levels. Additionally, it has been reported to reduce the number of rejection episodes in heart transplant recipients.

Lovastatin, simvastatin, and atorvastatin have all been used to successfully treat PTHL.<sup>[88-90]</sup> Lovastatin has been reported to produce sustained reductions of total cholesterol in renal graft recipients; however, an unusually high incidence of rhabdomyolysis has been reported in patients with heart transplants administered lovastatin.<sup>[89]</sup> The use of simvastatin has been reported to increase survival in heart transplant recipients.<sup>[23]</sup> Atorvastatin also has been reported to significantly reduce triglyceride levels in transplant patients.<sup>[91]</sup>

HMG CoA reductase inhibitors are thus effective in reducing total cholesterol and LDL-C levels with a good safety profile. A meta-analysis of 154 studies involving over 3000 transplant recipients receiving HMG CoA reductase inhibitors recently confirmed these findings.<sup>[92]</sup> Most transplant patients with PTHL will benefit from HMG CoA reductase inhibitor therapy, but fibric acid derivatives may be considered in those with hypertriglyceridaemia.<sup>[5]</sup> An additional benefit of HMG CoA reductase inhibitors is that they appear to have antirejection effects involving a decrease in antibody-dependent

**Table 1.** Hydroxymethylglutaryl coenzyme A reductase inhibitors ('statins')

Drug	Potential competition with CNI metabolism
Atorvastatin	Yes
Cerivastatin	Yes
Fluvastatin	No
Lovastatin	Yes
Pravastatin	No
Simvastatin	Yes

**CNI** = calcineurin inhibitors.

cytotoxicity as well as a suppression of natural killer cell function.<sup>[93]</sup>

5.3 Corticosteroid Withdrawal/Dose Reduction

Many centres have placed growing emphasis on the tapering or even discontinuation of corticosteroid therapy in recent years, particularly in patients given tacrolimus as a primary immunosuppressant.<sup>[94]</sup> However, cyclosporin regimens have also been evolving towards a reduced reliance on corticosteroids.

The benefits of corticosteroid withdrawal on the lipid profile of kidney graft recipients receiving cyclosporin-based therapy was recently studied by De Carlis and colleagues.<sup>[95]</sup> Triglyceride and total cholesterol levels were both significantly reduced in patients in whom corticosteroids were discontinued at 6 months, 1 year, and 2 years after randomisation. After 2 years, levels of total cholesterol, LDL-C, and triglycerides were 25.2, 32.7, and 26.6% lower and HDL-C levels were 18.6% higher in these patients compared with those who continued corticosteroids. Although a study by Hollander and colleagues<sup>[96]</sup> showed no differences in lipid profile despite successful corticosteroid withdrawal, this may have reflected differences between groups in the use of lipid-lowering therapies. Additionally, in a study by Ratcliffe and colleagues,<sup>[97]</sup> there was a sustained fall in the level of total serum cholesterol of more than 1 mmol/L with corticosteroid discontinuation.

Corticosteroid withdrawal has also been achieved in patients with stable liver transplants, receiv-



ing cyclosporin. Gomez and colleagues successfully discontinued corticosteroids in patients who were taking cyclosporin and azathioprine.<sup>[98]</sup> Fasting total cholesterol levels fell from 211 to 196 mg/dl. A reduction in triglyceride levels also occurred but was not significant.

In patients with stable grafts at least 1 year post-transplant, corticosteroid reduction and even withdrawal can be achieved in the majority of patients with a resultant improvement in lipid profiles. However graft function must be monitored carefully to avoid the danger of acute rejection. If complete withdrawal is inappropriate, a reduction to as little as 0.1 mg/kg/day would be expected to have a significant effect on PTHL and should be attempted if possible.

## 6. Conclusions

Although there currently is no consensus as to the correlation between PTHL and mortality or graft loss in the transplant recipient, there is widespread opinion that lipid abnormalities should be treated using guidelines similar to those used to the general population.

The calcineurin inhibitors, cyclosporin and tacrolimus are both associated with PTHL. Much of the purported difference between the 2 immunosuppressants as to the degree of hyperlipidaemia they cause appears to be the result of differences in doses of concomitantly used corticosteroids. Moreover in long term maintenance therapy, the lipid profiles seen with these 2 agents are indistinguishable. Overall, studies comparing the incidence and severity of PTHL between tacrolimus and cyclosporin have been based largely on single-centre and small-study population data, and have produced inconclusive results. Both tacrolimus- and cyclosporin-treated patients are at risk of PTHL, and should be treated when PTHL does occur.

The goal of treatment in transplant patients should be to restore a normal lipid profile. Given the magnitude of the problem posed by cardiovascular disease in these patients, more aggressive intervention is required and serious consideration should be given to treating the transplant recipient

as aggressively as the nontransplant patient for whom secondary prevention is needed. Finally a greater commitment to screening for cardiovascular risk factors prior to transplantation may ensure a more comprehensive management programme for the patient.

The mainstays of treatment for PTHL should be diet and lifestyle modification, reduction, or if appropriate, withdrawal of corticosteroids, and the use of lipid-lowering drugs. Pharmacological intervention should be primarily based on HMG CoA reductase inhibitors, which can provide an effective and well tolerated therapy for reducing lipid levels. Fluvastatin and pravastatin do not affect cyclosporin or tacrolimus blood concentrations and are preferred choices in transplant recipients taking calcineurin inhibitors. When hypertriglyceridaemia is a significant component of PTHL, atorvastatin or other therapies such as fibric acid derivatives may be appropriate. Additionally other medications capable of interfering with cholesterol metabolism should be administered with care and switched if appropriate.

In some patients, a normal lipid profile is not achieved despite the use of dietary measures, corticosteroid dose reduction (if possible), and lipid-lowering agents, and switching from one calcineurin inhibitor to another may be appropriate.

With the current therapeutic options and aggressive intervention, PTHL can be successfully treated in the majority of patients. And, if the management of cardiovascular risk in transplant patients generally can achieve the high standards that are now emerging for PTHL therapy, the benefit for long term patient survival may ultimately come to rival that achieved by antirejection drugs.

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