Post-transplant hyperlipidaemia

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Summary

The correction of post-transplant hyperlipidaemia warrants the judicious and timely use of pharmacological agents with dietary modification and exercise. Reduction in hyperlipidaemia may have some role in decreasing the incidence of chronic rejection of allografts. The awareness that the morbidity and mortality of atherosclerotic disease may be lowered by active intervention will result in a better quality of life for transplant recipients.

Keywords: transplantation, hyperlipidaemia, lipid-lowering drugs, atherosclerotic disease

In recipients of organ transplants, atherosclerotic vascular disease constitutes a major hurdle to long-term survival. In the general population, clinical trials, experimental, and epidemiological studies have effectively demonstrated the benefits of reducing lipids in arresting, or diminishing pre-existing coronary atherosclerotic lesions.¹ Measures to reduce plasma cholesterol are fundamental to the practice of preventative cardiology, and by corollary, should be the cornerstone of measures to reduce the continuing high morbidity and mortality in recipients of organ transplants.^{1–7}

A number of large-scale studies in both the normal population and 'at-risk' subjects have demonstrated the benefits of lowering cholesterol. Most recently, the West of Scotland trial has shown the beneficial effect of reducing hypercholesterolaemia in healthy men at high risk for coronary heart disease.⁸ This was the latest in a series of clinical trials which essentially confirmed the result of previous studies, most notably, the Los Angeles Veterans Diet trial, the WHO Clofibrate trial, the Lipid Research Clinics Cholestyramine trial, and the Helsinki Heart trial.⁹ The Scandinavian Simvastatin Survival study provided further evidence of the beneficial effects of reducing cholesterol – a 42% reduction in the risk of coronary death in simvastatin-treated subjects.¹⁰

Immunosuppressive regimens comprising steroids, cyclosporin and FK506 (Prograf, tacrolimus) have significant diabetogenic properties.¹¹ In addition, the great majority of transplant recipients have hypertension. These additional factors may alter the course of atherosclerosis, which is likely to be more aggressive than that of the general population.

The incidence of post-transplant hyperlipidaemia (PTHL) has varied from 22% to 54%, although some of this variation may be due to the lack of standardisation in reporting of the lipid levels. Vathsala *et al*¹² compared the effects of three different immunosuppressive protocols on hypercholesterolaemia in kidney transplant recipients; patients receiving Imuran–prednisolone had a 42.2% incidence versus 26.3% in the cyclosporin–prednisolone group; in heart transplant recipients, total cholesterol was greater in patients receiving cyclosporin–prednisolone therapy versus patients receiving cyclosporin–Imuran therapy.¹³ In our study of liver transplant recipients, PTHL was seen in 58%. More significantly, 37% of recipients had both post-transplant diabetes mellitus and hyperlipidaemia.¹⁴ It can be assumed that at least 50% of transplant recipients will have significant abnormalities of serum lipids.

Decisions about treatment of PTHL must be based on multiple factors, such as the assessment of risk, extent of benefits, cost, side-effects of medications, and possible interactions of immunosuppressants with drugs used to lower serum lipids. Furthermore, the emerging role of hypercholesterolaemia as a risk factor for chronic graft rejection must also be taken into account when initiating therapy for PTHL.

Synopsis of proposed mechanisms

HYPERLIPIDAEMIC EFFECTS OF STEROIDS

There is convincing evidence that long-term therapy with steroids increases both cholesterol and triglyceride levels. Steroids promote insulin resistance with a secondary hyperinsulinaemia and increase the hepatic secretion of very low density lipoproteins (VLDL). The latter effect is due to a reduction in lipoprotein lipase activity, and overproduction of triglycerides by the liver.¹⁵

HYPERLIPIDAEMIC EFFECTS OF CYCLOSPORIN AND FK506

A number of studies have shown that cyclosporin increases the total plasma cholesterol and triglyceride levels in the heart, liver, and kidney of transplant recipients. The mechanisms of its adverse effect on serum lipids is multifactorial. Cyclosporin may interfere with bile acid synthesis by inhibiting 26-hydroxylase (the first step in the side-chain oxidation of intermediates of the bile acid pathway), thereby limiting cholesterol degradation. It also decreases the uptake of low-density lipoprotein (LDL)-cholesterol, and may down-regulate

Target lipid levels

- LDL cholesterol less than 100 mg/dl
- HDL cholesterol greater than or equal to 35 mg/dl
- triglycerides less than 140 mg/dl

Box 1

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the hepatocyte membrane LDL receptor.¹⁶ Experimental studies have shown that cyclosporin stimulates cholesterol synthesis by increasing 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity, and also decreases the activity of lipoprotein lipase which reduces the clearance of VLDL and chylomicrons, resulting in hypertriglyceridaemia.¹⁷ FK506 was associated with increased oxidation of LDL; an important element in the pathogenesis of atherosclerosis.¹⁸

Another mechanism by which cyclosporin causes hypercholesterolaemia is by impairing the secretion of biliary phospholipids; chronic rejection in recipients of liver transplants may additionally induce PTHL by causing cholestasis. The role of genetic factors is not clear, however, and it is possible these may be unmasked after transplantation. In a randomised, double-blind trial of cyclosporin in the treatment of amyotrophic lateral sclerosis, cyclosporin was associated with raised total and LDL-cholesterol, but did not significantly affect triglycerides.¹⁹

Chronic liver disease is associated with deranged lipid metabolism. Liver transplantation has been shown to normalise cholesterol, phospholipids, lecithin-cholesterol acyltransferase, and apolipoprotein A-1.²⁰ Caution must, therefore, be exercised in ascribing elevations in lipids compared to pre-transplant 'baseline levels' to an adverse drug effect.

Mycophenolate mofetil (RS-61443, Cellcept) and Imuran did not have any adverse effect on serum lipid or sugar.²¹ However, it is possible that their steroid-sparing properties will result in a decreased incidence of metabolic complications in the long-term.

HYPERLIPIDAEMIC EFFECT OF RAPAMYCIN

Rapamycin (Sirolimus), a macrolide, has a structure similar to FK506, and will probably have a similar toxicological profile to FK506. It was shown that stable renal transplant recipients had derangement of serum lipids, of which elevated cholesterol level was significant in the rapamycin group, although triglyceride was not affected.²² The results of the Phase II trials are awaited, the precise mechanism by which rapamycin causes hyperlipidaemia is not clear.

Effect of cumulative dosages of steroids and cyclosporin on PTHL

The cumulative dosages of steroid and cyclosporin have been found to correlate with increased cholesterol levels. To study the influence of steroids and cyclosporin on PTHL in 71 consecutive liver transplant recipients, we calculated the total dosages of each drug in one year. The median requirement of steroid was 8000 mg, and of cyclosporin was 150 g. The mean steroid dose for patients who developed PTHL was significantly higher ($p=0.05$). Patients who developed PTHL had greater but not significantly greater cyclosporin dosages than those who did not (177.6 g *vs* 152.3 g, $p=0.14$). Patients with cholestatic liver diseases started with higher cholesterol levels, but the post-transplant course was similar.¹⁴

Hyperlipidaemic effects of cyclosporin versus FK506

Several studies have shown that liver transplant recipients receiving FK506 have better lipid profile than those receiving cyclosporin-based therapy.^{23,24} It needs to be clarified whether PTHL *per se* is an indication for switching from cyclosporin to FK506.

In a randomised, prospective trial,²⁵ we compared the effects of cyclosporin and FK506 both with concomitant low-dose steroids, on serum lipids in 63 liver transplant recipients, taking into account the effects of concomitant hyperglycaemia, administration of diuretics and antihypertensives, and glomerular filtration rate. Compared with pre-operative values, cyclosporin-treated patients were associated with significantly higher triglycerides at one, six and 12 months. FK506 was associated with a moderate reduction in cholesterol ($p=0.1$) and LDL ($p=0.06$) but had no effect on triglycerides and high density lipoproteins (HDL). At six and 12 months, triglycerides, cholesterol, and LDL were significantly lower in the FK506 than in the cyclosporin group. HDL levels were similar in both groups. The FK506 group of patients had a statistically significantly ($p<0.0001$) lower steroid usage for induction, maintenance, and in the total requirement over one year, but there was no significant difference in the steroid usage for the treatment of rejections (table). The incidence of hyperglycaemia, and of insulin dependence were similar in both groups; in no patient was the immunosuppressive regimen altered because of diabetes. Neither glomerular filtration rate nor blood glucose measurements correlated with PTHL. There was no

Table Comparison of steroid administration in the two treatment groups during the 12-month study²⁵

	<i>Cyclosporin (n=33)</i>	<i>FK506 (n=30)</i>	<i>p</i>
Total steroids administered (mg)	9190 ± 1992	65817 ± 2958	<0.0001
For induction (mg)	1600	1209 ± 248	<0.0001
For rejection (mg)	2722 ± 1739	2375 ± 1910	ns
For daily maintenance (mg)	4868 ± 630	3003 ± 1311	<0.0001

correlation between drug levels and serum lipids; no patient in either group developed myocardial infarction or stroke. Graft survival in both groups was comparable.

An effort must be made to minimise steroid dosage in transplant recipients in general, but particularly in those who have PTHL. Several studies from liver transplant centres have shown that patients receiving FK506 have lower cholesterol levels than those receiving cyclosporin.^{26,27} Newer agents such as mycophenolate mofetil, rapamycin, brequinar, and deoxyspergualin, will come under scrutiny for their metabolic effects.

Investigators reported that renal function was improved and serum lipids were normalised by switching from cyclosporin to Imuran in recipients of kidney transplants; however, when such a policy was used in recipients of liver transplants to improve or salvage renal function, there was an unacceptably high incidence of rejections.²⁸ Therefore, utmost care should be exercised when the 'mainstay' immunosuppressive agent such as cyclosporin or FK506 is withdrawn in order to correct PTHL.

Effect of diabetes mellitus on serum lipids

Transplant recipients who have both post-transplant diabetes and PTHL are at a particularly high risk for atherosclerotic complications. Overt diabetes in the general population increases the risk for cardiovascular disease by 2–4-fold, and in persons with noninsulin-dependent diabetes mellitus (NIDDM) up to 75% of deaths are attributed to ischaemic heart disease or other vascular disease.²⁹ However, the link between milder degrees of glucose intolerance and cardiovascular disease is less well established. More recently, studies have described an advanced glycosylation end-product modification of LDL, diminished clearance of which could contribute to dyslipidaemia and atherosclerosis.³⁰

There is a commonly seen association between hypertriglyceridaemia of diabetes and insulin resistance.³¹ There is evidence that triglyceride-rich lipoproteins may interfere with insulin action; a reduction in triglyceride levels was noted on the use of the recently introduced drug, metformin.³² It has also been shown that diabetic patients with hypertriglyceridaemia may have other genetic abnormalities of lipid metabolism such as lipoprotein lipase mutations.³³ Investigators have suggested the association of diabetes with increased free radical generation leading to the increased oxidation of LDL³⁴; increased rates of nonenzymatic glycosylation of LDL apolipoprotein B is thought to render LDL more susceptible to peroxidation³⁵ leading to atherosclerosis.

Studies have shown that meticulous control of diabetes will result in higher levels of HDL and lower levels of cholesterol due to the increased activity of lipoprotein lipase activity.³⁶ However, in patients with NIDDM, there is a persistence of dyslipidaemia as insulin resistance continues to be a dominant factor despite treatment with insulin or sulfonylureas, however, this situation may change with the recent introduction of metformin in clinical practice. Patients with NIDDM frequently present with low levels of HDL, and as low levels of HDL seem to predict the early development of cardiovascular disease, efforts should be made to raise HDL levels.³⁷

The Diabetes Control and Complications Trial provided persuasive evidence that tight control of glucose with insulin in patients with IDDM markedly reduced the incidence of microvascular complications³⁸; similar beneficial effects may be expected in the NIDDM patients. When instituting intensive insulin regimens for post-transplant diabetes mellitus, the adverse effects of an intensive insulin regimen such as weight gain and increase in hypoglycaemic episodes must be kept in mind. Furthermore, the atherogenic potential of 'overinsulinisation' has been a cause for concern; however, sufficient evidence does not exist to implicate insulin as a cardiovascular risk factor.³⁹ The goal should be to achieve near-normal glycaemia (glycohaemoglobin level no more than 1% above the upper normal limit) initially by diet

and exercise therapy, followed by oral hypoglycaemic agents, and finally insulin regimens. Some beta-blockers and diuretics which tend to lower HDL levels should be avoided. Alternative antihypertensive agents such as vasodilators and angiotensin-converting enzyme (ACE) inhibitors may be considered. The use of statins and fibrates has been advocated to raise HDL. However, studies have shown that niacin was the only drug to achieve substantial elevations of HDL to near-normal levels and niacin can result in glucose intolerance. Further studies are indicated to evaluate the role of combination therapy in transplant recipients who have both diabetes and PTHL. Comprehensive care must also include aggressive attempts to reduce cardiovascular risk factors such as hypertension, smoking, dyslipidaemia, and obesity, by a multidisciplinary team approach.

Hypercholesterolaemia as a risk factor for graft rejection

There are interesting data that implicate atherosclerosis in chronic graft rejection.⁴⁰ Experimental studies have shown that hypercholesterolaemia accelerated the development of proliferative vascular lesions such as seen in chronic rejection; abnormal lipoprotein patterns in kidney transplant recipients were associated with acute and chronic rejection.⁴¹

Numerous theories have been suggested to explain the association between abnormalities in lipids and vascular intimal hyperplasia. LDL *in vitro* was shown to upregulate class II antigen expression, and acted as a chemotactic agent for monocytes.⁴² Furthermore, LDL was shown to have a direct toxic action on endothelial cells, and to accelerate atherogenesis by inducing the macrophages to form foam cells.⁴³

HMG-CoA reductase inhibitors may have beneficial effects on the transplanted organ, independent of their lipid-lowering effects. Simvastatin was reported to decrease the incidence of coronary heart disease in the rat heart allograft model,⁴⁴ perhaps by decreasing thromboxane production.⁴⁵ Pravastatin was shown to decrease acute rejection episodes in recipients of heart transplants.⁴⁶

There is a growing body of work which favours the use of omega-3 fatty acids (such as the use of fish oils), and HMG-CoA reductase inhibitors as adjunctive agents in reducing the incidence of graft rejection. However, in a recent retrospective study in 665 consecutive renal transplant patients (receiving cyclosporin, prednisolone and Imuran), PTHL did not correlate with the number of rejection episodes, serum creatinine, or graft survival.⁴⁷ In view of contradictory reports, a prospective trial will be necessary to provide a definitive answer to this question. These agents will certainly be less toxic than some of the currently available immunosuppressants used in the treatment of chronic rejection.⁴⁸

Treatment

The National Cholesterol Education Program (NCEP) panel recommended that total cholesterol and HDL-cholesterol be measured in all adults 20 years or older at least every five years.⁴⁹ In recipients of transplants, the recommendations must surely be more stringent; a full lipid profile pretransplant and every six months thereafter. The objections to screening are cost factors, psychological impairment, and risks associated with inappropriate intervention.⁵⁰

The NCEP panel recommended that drug treatment should be initiated in patients with coronary heart disease who have serum LDL-cholesterol greater than 130 mg/l, with a goal of reducing them to less than 100 mg/l. Low HDL-cholesterol concentrations in patients with established coronary heart disease has been shown to accurately predict an adverse outcome. Therefore, therapy to reduce plasma LDL and total cholesterol concentrations should be accompanied by measures to raise HDL concentrations. Even in patients who have normal total and LDL-cholesterol, attempts to raise a low HDL-cholesterol by exercise, weight loss, or drugs should be recommended.

A group from Sheffield, UK, has described a scoring system⁵¹ for assessing the coronary risk in the general population which may be applicable to transplant recipients. They analysed the effect of hypertension, smoking, diabetes, left ventricular function, age, and cholesterol concentration. By using a logistic regression equation predicting coronary risk derived from the Framingham population, they found that men were at a higher risk than women, and age had a dominant effect on the degree of coronary risk. Their study highlighted the fact that lipid-lowering drugs may not be indicated in some patients with a high cholesterol levels; benefit from pharmacological intervention should be based on the measurement of coronary risk, and not

merely on serum cholesterol levels. Transplant recipients have a greatly increased risk due to the high incidence of diabetes, hypertension, and the ongoing need for immunosuppressants; therefore, such a table would be of considerable benefit as patients with seemingly normal cholesterol may still have a greatly increased risk of cardiovascular accidents.

Despite the inherent difficulties in obtaining a successful reduction in serum lipids in transplant patients, a reasonable result can be achieved by the judicious use of dietary modification and lipid-lowering drugs, such as nicotinic acid, cholestyramine, fibrates, and statins. In nephrotic patients in chronic renal rejection, an ACE inhibitor may reduce proteinuria, and thereby decrease LDL.

Dietary modification

Transplant recipients must be encouraged to follow the American Heart Association Step-One Diet, aimed at restricting the intake of saturated fat and cholesterol. A regular exercise programme, cessation of smoking, control of diabetes, and hypertension should also be essential components of post-transplant management.⁵² The risk-benefit ratio of certain drugs, such as oral contraceptives, antidepressants, anti-acne drugs, beta-blockers, thiazides, and anti-infectives, must be carefully assessed as these may have an adverse effect on lipids.

EFFECT OF DIETARY SUPPLEMENTATION WITH FISH OIL ON SERUM LIPIDS

The importance of dietary modification to alter the immune response has come from experimental and clinical studies. Rat heart allografts showed significantly increased survival when fed *n*-3 polyunsaturated fatty acid,⁵³ but some data pointed to the fact that improved graft survival was related to a decrease in the *n*-6 fatty acid content.⁵⁴ It is possible that the ratio of dietary *n*-3/*n*-6 fatty acids may be more important than absolute levels of individual fatty acids. It was shown that the immunoregulatory effect of pretransplant blood transfusion was mediated by altering the essential fatty acid composition,⁵⁵ and coronary atherosclerosis in the rat heart allograft model was slowed by administration of fish oil.⁵⁶ Omega-3 fatty acids are postulated to exert their immunomodulatory effect by multiple mechanisms: inhibiting the effect of interleukin (IL)-1, tumour necrosis factor, altering histocompatibility antigen (HLA-DR) expression, reducing vascular smooth muscle proliferation, and vascular permeability.⁵⁷

Reports have suggested that the administration of omega-3 fatty acids in the form of fish oil have improved renal haemodynamics and serum lipids in recipients of renal transplants. Furthermore, patients taking supplemental fish oil had better control of post-transplant hypertension, with fewer acute and chronic rejection episodes.⁵⁸⁻⁶⁸ However, most of these studies have been small and limited to a single centre. There is a strong case for a larger multicentre trial to define the role of fish oil supplementation in transplant recipients.

EFFECT OF DIETARY SUPPLEMENTATION WITH SOYA PROTEIN ON SERUM LIPIDS

A meta-analysis by Anderson *et al*⁶⁹ showed that in 34 of 38 clinical studies, serum cholesterol levels were reduced to a greater extent in patients treated with soya protein. Those subjects who had moderate-to-severe hypercholesterolaemia had a greater benefit than those persons with mild elevations of serum cholesterol. However, this interpretation has not been accepted by all researchers, as some studies did not show a reduction in LDL, and the effect on persons with mild hypercholesterolaemia (200 mg/dl or less) was not significant.⁷⁰ Indeed, the conclusion of the American Heart Association (1993, Diet-Heart Statement) was that the effect of soya protein intake on serum lipids in clinical trials was not convincing. Nevertheless, there are sufficient data in favour of the moderate use of soya protein as part of an overall balanced diet.

Lipid-lowering drugs for transplant recipients

The National Cholesterol Education Program suggested the use of cholestyramine and nicotinic acid as the first line of treatment for primary hypercholesterolaemia. Cholestyramine may interfere with the absorption of cyclosporin, however, it is not known whether the microemulsion form of cyclosporin (Neoral) may allow the concomitant use of cholestyramine. Furthermore, bile-acid-binding resins may cause constipation, sodium retention, and may increase triglycerides. Niacin was found to be effective in mixed hyperlipidaemias, but may cause multiple side-effects such as flushing, glucose intolerance, hyperuricaemia, and hepatotoxicity.

Lipid-lowering drugs

- the statins (HMG-CoA reductase inhibitors) are the most commonly used lipid-lowering agents in post-transplant hyperlipidaemia
- cholestyramine may interfere with the absorption of cyclosporin and FK506
- niacin may cause glucose intolerance and hyperuricaemia and is generally not well tolerated in posttransplant patients
- a high incidence of rhabdomyolysis was seen in heart transplant recipients who received lovastatin and cyclosporin
- gemfibrozil – a fibric acid derivative – can cause biliary stones in liver transplant recipients
- the comparative efficacy of the statins (fluvastatin, pravastatin, lovastatin and simvastatin) and the role of combination therapy (such as statin and gemfibrozil) is currently being evaluated

Fibric acid derivatives such as gemfibrozil was found to be effective in renal transplant recipients by reducing the cholesterol/HDL ratio; however, it was not recommended for use in liver transplant recipients because it increased the incidence of biliary stones.⁷¹ The statins (HMG-CoA reductase inhibitors) are the most commonly used lipid-lowering agents in transplant recipients. Kasiske *et al*⁷² used lovastatin in recipients of kidney transplants (receiving prednisone and Imuran) and showed that reductions in total and LDL-cholesterol levels were of the same magnitude as that reported in the treatment of primary hyperlipidaemias, but the increase in HDL was not significant. They did not find alterations in liver enzymes, or elevation of creatine kinase levels, although there was a significant increase of white blood cells, even when lovastatin was used in relatively low doses (20 mg/day). It is also alarming to note a high incidence of rhabdomyolysis in cardiac transplant recipients treated with cyclosporin and lovastatin,⁷³ but not in recipients of other organs.

Yoshimura *et al*⁷⁴ evaluated the effect of pravastatin (10 mg/day) and found that it was effective in reducing total cholesterol and LDL in renal transplant recipients; levels of HDL and triglycerides were unaffected with no adverse effect on the graft function or the creatine kinase levels. The effect of pravastatin was also evaluated in heart transplant recipients (receiving cyclosporin, prednisone, Imuran) in a randomised placebo-controlled study.⁷⁵ Pravastatin was given in the dose of 20 mg/day and increased to 40 mg/day when tolerated. At the end of a year cholesterol levels were significantly lower and there was a reduced incidence of rejections in the pravastatin group. Of great interest were the findings that in the control group of patients, there was a significantly increased intimal thickness and intimal index as assessed by intra-coronary ultrasonography. From this study it seems that statins caused an increased state of immunosuppression, although the precise mechanisms can only be speculated at the present time. It has been postulated that HMG-CoA reductase inhibitors decrease antibody-dependent cellular cytotoxicity and natural killer cell function.⁷⁶ Fluvastatin in recipients of renal transplants was seen to reduce total cholesterol by about 13%, LDL by about 22%, and Apo B by about 13% with no adverse effects on either cyclosporin levels, renal and liver function tests, or creatine kinase levels.⁷⁷

Massay *et al*⁷⁸ recently conducted a meta-analysis of 154 studies involving 3065 patients to compare the relative efficacy of antilipidaemic agents in patients with renal disease including recipients of renal transplants. Of the 29 study groups, 28 showed reduction in cholesterol, 24 in triglyceride levels, and eight showed reduction in LDL levels by dietary intervention. HMG-CoA reductase inhibitors were effective in reducing cholesterol and LDL in the majority of patients treated, but the reduction in triglyceride levels was not as effective. Interestingly, of the 14 patient groups who received fish oil, 12 groups showed a reduction in triglyceride levels. They concluded that low doses of statins were effective in lowering LDL; renal transplant recipients with high triglyceride levels and low HDL levels showed benefit with a fibric acid derivative.

The efficacy of all four HMG-CoA reductase inhibitors as monotherapy in lowering total cholesterol and LDL has been confirmed in numerous placebo-controlled trials. However, the comparative effects of these drugs have been difficult to evaluate because of multiple uncontrolled variables. Hsu *et al*⁷⁹ reviewed the comparative safety and efficacy of fluvastatin, pravastatin, lovastatin, and simvastatin. They found that on a mg-per-mg basis, simvastatin was twice as potent as lovastatin and pravastatin; the hypocholesterolaemic effect of fluvastatin appeared to be 30% less than that of lovastatin. In post-transplant patients receiving cyclosporin, lovastatin and simvastatin were seen to be safe, but pravastatin was considered the drug of choice at higher dosages because of its lower incidence of side-effects such as myopathy. Combination therapy consisting of HMG-CoA reductase inhibitor and gemfibrozil was recommended for patients with secondary or severe combined hyperlipidaemia, although the combination of lovastatin–gemfibrozil was associated with the development of rhabdomyolysis. Clinically significant side-effects were rare, and drug withdrawal because of clinical or laboratory adverse reactions were comparable among the four agents.

There is a strong case for aggressive management of PTHL as investigations have suggested that a 1% reduction in total cholesterol decreases the risk for ischaemic heart disease by 2% in individuals with primary hyperlipidaemia.⁸⁰ These data could be extrapolated to secondary hyperlipidaemia of transplant recipients. Risk assessment is important; lipid-lowering drugs should be one of the components of the overall strategy in reducing the incidence of cardiovascular disease. It is tempting to suggest the routine use of fish oil and soya protein in transplant recipients; however, evidence so far has come from only small studies.

Treatment of post-transplant hyperlipidaemia

- dietary modification
- exercise, cessation of smoking
- lipid lowering drugs
- correction of obesity, post-transplant diabetes, and hypertension
- steroid-reducing regimens should be considered in all transplant recipients
- dietary supplementation with fish oil and soya protein (not proven)

Steroid-reducing regimens in PTHL

Tapering or complete withdrawal of steroids in transplant recipients has been carried out successfully in some instances, but must be weighed against the possibility of an increased incidence of rejections. Hricik *et al*⁸¹ have shown that complete withdrawal of steroids was possible in kidney, and kidney–pancreas transplant recipients with substantial beneficial effect on serum lipids. Hariharan *et al*⁸² showed that steroid withdrawal in 94 of 121 kidney transplant recipients receiving Imuran and cyclosporin in addition to prednisone resulted in a decrease in total cholesterol and LDL, although seven patients had breakthrough rejections and needed re-introduction of steroids. Similarly, steroid therapy could be withdrawn in 33 of the 67 paediatric kidney transplants with a reduction of total cholesterol, but 19 of these patients had to be restarted on prednisone.⁸³

Attempts to substitute Imuran for prednisone have been made by investigators both for post-transplant diabetes and hyperlipidaemia. However, these attempts have also resulted in increased rejections, and prednisone had to be restarted in many patients.⁸⁴ A further concern is the danger of myelosuppression with Imuran when it is increased to compensate for reduced dosages of prednisone, leading to the suggestion that prednisone should not be withdrawn in patients tolerating less than 1.5 mg/kg/day of Imuran.⁸⁵ However, steroid withdrawal for PTHL was more successful in liver transplant recipients who were stable and did not have recent rejection episodes.^{86,87} Protocols for complete steroid withdrawal will need to be more stringent; perhaps applicable to only a small subgroup of transplant recipients, and the timing of steroid withdrawal may be critical.^{88–92}

Alternate-day steroid therapy is an attractive alternative to complete withdrawal of steroids. Curtis *et al*⁹³ found that patients receiving alternate-day prednisone had a significant decrease in the total cholesterol, while Cattran *et al*⁹⁴ found a beneficial effect on triglyceride levels when a similar protocol was used. It would seem reasonable to institute alternate-day steroids in stable transplant recipients at some point after transplantation, however, larger trials are needed to study the validity of alternate-day steroids in normalising serum lipids in transplant recipients. The availability of mycophenolate mofetil, FK506, and rapamycin may allow for adequate immunosuppression with lower or alternate-day steroid protocols.

Role of pancreas transplantation in reducing serum lipids

Combined vascularised pancreas–kidney transplantation is now a viable option for patients with end-stage renal disease and type I diabetes. Experimental and clinical studies have revealed a secondary beneficial effect on the lipid profile,⁹⁵ although studies to show regression or stabilisation of large vessel disease would require large numbers of patients for adequate randomisation.⁹⁶ Further improvements in the techniques of pancreatic islet-cell transplantation are awaited for the widespread application of the combined procedure.⁹⁷

Natural history of hyperlipidaemia in transplant recipients

Controlled studies in patients who have had an acute myocardial infarction have shown that lipid-lowering drugs reduce the mortality and re-infarction compared to placebo.^{9,10,98–100} Furthermore, lipid-lowering agents were shown to have a favourable effect on coronary artery lesions and cardiac events.¹⁰¹ Although dietary therapy to correct lipid abnormalities was recommended as the first line of treatment in these trials, lipid-lowering agents were also necessary in most patients.¹⁰²

A recently completed, controlled, and widely cited trial, in the general population convincingly demonstrated that reduction of hypercholesterolaemia by diet and pravastatin reduced the incidence of subjects undergoing myocardial re-vascularisation procedures, and also reduced the risk of cardiovascular mortality without increasing the risk of death from non-cardiovascular causes. The subjects were asymptomatic (no previous myocardial infarction) men between 45–64 years, and had a mean total cholesterol of 272 mg/dl.⁸ Similar studies in post-transplant recipients are lacking; however, these results can be extrapolated to transplant recipients who have cholesterol levels in a similar range.

Some recent data also suggest that PTHL may be organ specific; liver transplant recipients have a lesser degree of hyperlipidaemia than recipients of renal or heart transplants.¹⁰³ In particular, coronary lesions from explanted heart allografts demonstrated massive lipid accumulation in the early post-

Summary points

- transplant recipients have a triple risk for cardiovascular accidents: hyperlipidaemia, hypertension, and post-transplant diabetes
- correction of each of these factors will lead to a reduction of cardiovascular and neurovascular morbidity and mortality
- at least 50% of all transplant recipients will have significant hyperlipidaemia
- hypercholesterolaemia may also be a risk factor for chronic graft rejection
- hyperlipidaemia may be organ specific; heart transplant patients are more susceptible than liver transplant recipients

Box 4

transplant period, which probably contributed to severe intimal thickening.¹⁰⁴ It is, however, generally agreed that a large multicentre trial is necessary to assess the risk:benefit ratio of treating transplant recipients and thereby decreasing the incidence of cardiovascular disease. The cost and side-effects of lipid-lowering agents should also be assessed in such a trial. The study of the natural history of PTHL may, however, be complicated by the fact that patients with renal failure and cholestatic liver disease may have cardiovascular co-morbidity that may be difficult to correct after transplantation.

Future directions

The ideal drug therapy for lowering serum lipids in the transplant recipient needs to be defined. A large multicentre trial will be needed to determine the optimal drug with the least side-effects, minimum drug interactions, and a positive effect on chronic allograft rejection.

The dangers of aggressive use of cholesterol-reducing agents should be balanced against the possibility of an increased incidence of psychiatric disorders and malignancies. Despite the concern about increased mortality associated with a low plasma cholesterol concentration, there was no evidence of a 'J-shaped' relationship between the total cholesterol concentration and mortality.¹⁰⁵

The development of immunosuppressants of maximum effectiveness with the least metabolic adverse effects should be the next goal. Novel strategies such as administration of folic acid to reduce plasma concentration of homocysteine,¹⁰⁶ and genetic aspects of hyperlipidaemia are areas of research which may be of relevance in the treatment of PTHL.¹⁰⁷

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