MINIREVIEWS

Lipids in liver transplant recipients

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Abstract

Hyperlipidemia is very common after liver transplantation and can be observed in up to 71% of patients. The etiology of lipid disorders in these patients is multifactorial, with different lipid profiles observed depending on the immunosuppressive agents administered and the presence of additional risk factors, such as obesity, diabetes mellitus and nutrition. Due to recent improvements in survival of liver transplant recipients, the prevention of cardiovascular events has become more important, especially as approximately 64% of liver transplant recipients present with an increased risk of cardiovascular events. Management of dyslipidemia and of other modifiable cardiovascular risk factors, such as hypertension, diabetes and smoking, has therefore become essential in these patients. Treatment of hyperlipidemia after liver transplantation consists of life style modification, modifying the dose or type of immunosuppressive agents and use of lipid lowering agents. At the start of administration of lipid lowering medications, it is important to monitor drug-drug interactions, especially between lipid lowering agents and immunosuppressive drugs. Furthermore, as combinations of various lipid lowering drugs can lead to severe side effects, such as myopathies and rhabdomyolysis, these combinations should therefore be avoided. To our knowledge, there are no current guidelines targeting the management of lipid metabolism disorders in liver transplant recipients. This paper therefore recommends an approach of managing lipid abnormalities occurring after liver transplantation.

Core tip: Lipid disorders after liver transplantation are common and can significantly increase the risk of cardiovascular events in liver transplant recipients. Furthermore, dyslipidemia may also impair graft function and survival. Therefore management of dyslipidemia is of great importance in preventing cardiovascular diseases and graft dysfunction in these patients. Knowledge of the different manifestations of lipid disorders after liver transplantation, the role of immunosuppressive agents and of drug-drug interactions is therefore essential for management and

follow-up of these patients.

INTRODUCTION

Hyperlipidemia (HLP) is considered one of the most important risk factors for the development of athero-sclerosis. The prevalence of HLP in liver transplant (LT) recipients is high and has been estimated to vary from 27% to 71%[1,2].

Development of HLP is multifactorial, including in LT recipients. Immunosuppressive agents administered after liver transplantation may lead to lipid metabolism disorders and HLP. Although some studies have reported that immunosuppressive therapy is not a risk factor for cardiovascular events[1], others have found that the adverse event profiles of immunosuppressive agents can contribute to cardiovascular risk in transplant recipients[3,4].

A meta-analysis reporting pooled estimates from population-based and nested case-control studies found that post-LT recipients have an approximately 64% greater risk of cardiovascular events than the general population[5]. Although the increased risk for atherosclerosis-associated events in transplant recipients suggests that all of these patients be treated prophylactically with lipid lowering drugs, drug interactions and other side effects limit this approach. In practice many transplant physicians remain cautious about treating LT recipients with lipid lowering drugs.

Cardiovascular diseases are emerging as the main cause of non-graft-related mortality in LT recipients, especially in older subjects, thus affecting their long-term outcomes and causes of death[6,7]. Optimal follow up of these patients should include continuous observation and management of cardiovascular risk factors such as dyslipidemia.

Post-LT HLP, however, occurs frequently after LT, independent of administration of immunosuppressive agents[8]. Additional causes of HLP include increased body weight, malnutrition, abnormal renal function, impaired glucose metabolism and genetic predisposition. Since genetically associated HLP also occurs in the general population, HLP may also result from a liver donor carrying, *e.g.*, a low-density lipoprotein-cholesterol (LDL-C) receptor deficient variant or an apolipoprotein E defective variant expressed by the liver[9,10]. To date, guidelines have not been formulated for the prevention and treatment of lipid metabolism disorders after LT. Based on the recommendations of the 2011 guidelines formulated by the Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)[11], in addition to the guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA)[12], and our practical experience treating LT recipients, we here propose strategies to manage dyslipidemia in this patient population.

HLP classification

Various types of HLP have been identified, including HLP with increased triglycerides (hypertriglyceridemia), HLP with high LDL-C (hypercholesterolemia) and their combination, HLP with both hypertriglyceridemia and hypercholesterolemia. Statin treatment should be tailored to the type of HLP, as these agents, when administered independent of the type of HLP, may result in reduced efficacy and metabolic control, a secondary increase in triglycerides, and increased side effects.

LDL-C and atherogenesis

Epidemiological studies have shown that HLP with high serum LDL-C is a particular risk factor for the development of atherosclerosis[13,14]. Table 1 shows the relationship between LDL-C concentrations and potential atherogenicity in the general population. Indications for treatment of LT recipients with lipid lowering drugs depend on each patient's individual risk profile.

Cardiovascular risk shows a greater association with serum LDL-C than total cholesterol concentrations. Hypercholesterolemia may also be due to increases in serum high density lipoprotein-cholesterol (HDL-C) concentrations, which have no clinical relevance.

Alterations in diet may show have moderate effects on serum LDL-C concentrations, but they are often not sufficient. Familial hypercholesterolemia, for example, does not significantly respond to dietary approaches. Cardiovascular events such as myocardial infarction can occur as early as the fourth to sixth decade of life in the absence of lipid lowering treatment. Most trials of lipid-lowering agents have assessed response to therapy by measuring serum LDL-C concentrations, indicating the importance of reducing serum LDL-C concentrations in managing dyslipidemia. A meta-analysis by the Cholesterol Treatment Trialists' Collaboration of several trials involving > 170000 patients also showed that lowering LDL-C concentration reduced the risk of cardiovascular disease (CVD)[15]. Moreover, reducing LDL-C concentration to below 1.8 mmol/L (below approximately 70 mg/dL), or to < 50% of baseline, was optimal in reducing the risk of CVD[15].

HYPERTRIGLYCERIDEMIA AND ITS METABOLIC IMPACT

Metabolic complications occur frequently in patients with hypertriglyceridemia, with long-term hypertri-

Table 1 Hypercholesterolemia and its estimated atherogenic potential[25]	
LDL-cholesterol (mg/dL)	
< 100	Optimal
100-129	Near/above optimal
130-159	Borderline high
160-189	High
⩾ 190	Very high

LDL: Low density lipoprotein.

Table 2 Hypertriglyceridemia and its estimated atherogenic potential[25]	
Triglycerides (mg/dL)	
< 150	Optimal
150-190	Near/above optimal
200-499	High
⩾ 500	very high

Table 3 Proposed targeted triglyceride serum concentrations in liver transplant recipients[42]
Triglyceride-targets and -limits
Triglyceride-targeted serum concentrations < 200 mg/dL
Triglycerides < 400 mg/dL with life-style intervention[1]: tolerable
Triglycerides < 500 mg/dL despite lipid-lowering medication before start of immunosuppression: no initiation of therapy with mTOR-inhibitors
Triglycerides > 500 mg/dL under mTOR-inhibitors: if despite therapy triglycerides < 500 mg/dL, change to different group of immunosuppressant (or reduce doses)

[1]Life-style modification/ therapy (lipid-lowering medication): (1) weight loss; (2) increase physical activity; (3) optimize glucose-metabolism; and (4) lipid lowering agents. mTOR: Mammalian target of rapamycin.

glyceridemia often causing lipomatosis of the liver and pancreas[16]. These pathological alterations may impair glucose metabolism, especially peripheral insulin resistance, resulting in diabetes mellitus[16]. Table 2 shows a classification of serum triglyceride concentrations in the general population, and Table 3 shows serum concentration limits and treatment recommendations with mTOR inhibitors in LT recipients.

Specific treatment targets for hypertriglyceridemia have not yet been determined. Moreover, serum triglyceride concentrations are highly variable, increasing during the day in most individuals. Treatment to reduce the risk of pancreatitis, however, is recommended when serum triglyceride concentrations exceed 1000 mg/dL[17]. Causes of elevated serum triglyceride concentrations include obesity, alcohol consumption, high carbohydrate diet, diabetes mellitus, reduced kidney function, nephrotic syndrome; treatment with steroids[18], protease inhibitors, hormone substitutes, calcineurin inhibiting drugs[19], mTOR inhibiting drugs[20]; and predisposing genetic factors. In contrast to elevated

LDL-C levels, hypertriglyceridemia can be influenced by diet. A weight loss of 2-3 kg can result in a significant reduction in serum triglyceride concentrations, of up to 200 mg/dL[21]. In contrast, a weight loss of more than 10 kg may reduce serum LDL-C concentrations by only 30 mg/dL. Fruit juices and other high-carbohydrate products, as well as small amounts of alcohol, may exacerbate hypertriglyceridemia temporarily.

COMBINED HLP

Treatment of patients with combined HLP depends on serum LDL-C and triglyceride concentrations and their risks of atherosclerosis and metabolic symptoms. As combinations of lipid-lowering agents may cause side effects, including rhabdomyolysis, both atherosclerosis and metabolic risks must be evaluated. Based on a patient's individual risk profile, we recommend lipid lowering treatment targeting either LDL-C or triglyceride concentrations. Combinations of drugs that lower serum cholesterol and triglyceride concentrations should be avoided in LT recipients due to their interactions with immunosuppressants. Liver enzymes and creatinine kinase should be measured weekly in patients started on both cholesterol and triglyceride lowering drugs.

Lipoprotein (a) and atherogenesis
Lipoprotein (a) [Lp(a)] is a risk factor for atherogenesis and may play roles in plasma viscosity and the coagulation cascade[22-24]. Lp(a) should be monitored regularly in patients with myocardial infarction and other cardiovascular end points such as cerebral insult. Serum Lp(a) concentrations < 30 mg/dL are regarded as normal. Elevated serum Lp(a) concentrations in patients with hypertriglyceridemia may respond to dietary modifications or treatment with nicotinic acid. However, statin treatment of patients with elevated Lp(a) and LDL-C does not significantly reduce Lp(a) concentrations. LDL-apheresis may be successful in treatment of patients with persistently high LDL-C and/ or Lp(a). In Germany, LDL-apheresis is currently used to treat selected patients with manifest atherosclerosis and Lp(a) > 60 mg/dL.

HDL-C
Serum HDL-C concentration < 40 mg/dL is a known risk factor for coronary heart disease[11,25]. High serum HDL-C does not protect against atherosclerosis in patients with high serum LDL-C (Table 4)[26]. High serum triglyceride concentrations, overweight, obesity and a high carbohydrate diet may reduce serum HDL-C concentrations. Life style modifications, triglyceride lowering and antidiabetic interventions can improve and normalize serum HDL-C.

DIAGNOSTICS OF LIPID STATUS
Serum lipid concentrations should be measured in a

Table 4 Serum high density lipoprotein-cholesterol concentrations and predicted atherogenic impact[25]

HDL-cholesterol (mg/dL)	
> 60	Optimal
40-60	Near optimal
< 40	Atherogenic

HDL: High density lipoprotein.

Table 5 Criteria of the metabolic syndrome (3 of 5 criteria have to be fulfilled)[25]

Risk factor	Limit value
Abdominal obesity	Abdominal measurement
Men	> 120 cm
Women	> 88 cm
Triglycerides	≥ 150 mg/dL
HDL-cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/ ≥ 85 mmHg
Fasting blood sugar or insulin-glucose tolerance test after 60, 120 and 180 min	≥ 110 mg/dL

fasting state. Postprandial synthesis of chylomicrons may increase serum cholesterol and especially triglyceride concentrations. Total serum cholesterol concentration is the sum of serum HDL-C, LDL-C, and very low density lipoprotein (VLDL)-C concentrations.

Targets for lipid lowering agents include serum LDL-C, total cholesterol (TC) and non-HDL-C concentrations. The 2011 ESC/EAS guidelines have reported that most studies of lipid lowering therapy strategies determine risk by measuring serum TC and LDL-C concentrations. Many clinical trials have shown that reducing TC or LDL-C, even in high-risk-patients, is associated with statistically and clinically significant reductions in cardiovascular mortality[11]. In addition, the 2013 ACC/AHA guidelines have targeted serum LDL-C, TC and non-HDL-C in reducing the risk of atherogenesis.

Non-modifiable risk factors for coronary heart disease include age, sex (male) and genetic factors (family history). Modifiable risk factors for cardiovascular events include arterial hypertension, nicotine consumption (smoking), diabetes mellitus, dyslipoproteinemia (high LDL-C, low HDL-C), obesity and physical inactivity. Measurement of serum lipid concentrations, evaluation of risk factors and diagnosis of glucose metabolism disorders can identify patients with metabolic syndrome (Table 5). Table 6 shows proposed target serum LDL-C concentrations as a function of individual risk factors. These patients have an increased risk of developing insulin resistance and subsequent cardiovascular events, suggesting they be regularly monitored for cardiovascular risk factors.

CHARACTERISTICS OF LIVER TRANSPLANT RECIPIENTS

Risk factors for atherosclerosis and cardiovascular events in LT recipients are qualitatively the same as those in the non-transplant population. Quantitatively, LT recipients are at abnormally high risk for the development of atherosclerosis and metabolic dysfunction than the non-transplant population. For example, the reported rate of coronary heart disease in LT recipients is 30%[27], compared with 9% in the general population[28].

Due to the increased life expectancy of LT recipients, it has become a challenge to manage metabolic disorders, which are also associated with immunosuppressive agents in these patients. Therefore, recommendations for lipid management in LT recipients are urgently required, including the consideration of additional cardiovascular risk factors and the effects of immunosuppressive agents.

Table 6 shows targeted serum LDL-C concentrations in LT recipients. These concentrations are dependent on patient risk category. Long-term serum LDL-C concentrations > 160 mg/dL should be avoided. Patients should begin by modifying diet and life style for at least three months; if serum LDL-C concentrations remain higher than recommended, patients would be started on lipid reducing agents.

IMMUNOSUPPRESSIVE THERAPY AND THE DEVELOPMENT OF HLP

HLP has been observed in up to 45% of LT recipients, regardless of immunosuppressive medication[8], and recent studies have reported HLP in 32%-49% of LT recipients after 10-23 mo[29-33]. Hypercholesterolemia has been reported in 13%-46% of LT recipients after 11-20 mo[34-36], and hypertriglyceridemia has been observed in 15%-50% of patients after 11-12 mo[35,36]. Many factors can influence the development of HLP in these patients, including nutrition, body weight, renal function, glucose metabolism, and genetic factors.

Immunosuppressants, including steroids and calcineurin inhibitors, have been shown to interfere with lipid metabolism and increase the risk of hyperlipidemia. Steroid treatment has been associated with both diabetes mellitus and dyslipidemia[37]. Steroids upregulate the synthesis of fatty acids, resulting in peripheral insulin resistance and increased VLDL-C synthesis within the liver. This can result in both isolated hypertriglyceridemia and combined HLP. Serum cholesterol concentrations are increased by activation of multiple indirect pathways. Hyperinsulinemia may stimulate VLDL-C synthesis in the liver, as well as downregulating LDL receptors, possibly by suppression of adrenocorticotropic hormone[38].

Table 6 Proposed low density lipoprotein-cholesterol-serum concentrations and limits for therapeutic interventions[25]			
Risk category	LDL-targeted serum concentration (mg/dL)	Life style modification[1,2] starting at LDL-serum concentrations (mg/dL)	Medical treatment
CHD, PAD, CVD[3]	< 100	⩾ 100	⩾ 130
⩾ 2 risk factors	< 130	⩾ 130	⩾ 160
0-1 risk factor	< 160	> 160	> 190

[1]Aspects of life style modification: (1) nutrition: (a) saturated fats < 7% of calories, dietary cholesterol < 200 mg/d; (b) increase of soluble fibers (10-25 g/d) and sterols of vegetable origin (2 g/d) as an option of lowering LDL-levels; (2) weight management; and (3) physical activity; [2]If LDL-serum concentrations after 3 mo still elevated, consider medical treatment; [3]Documented vascular atherosclerosis. CHD: Coronary heart disease; CVD: Cardiovascular disease; LDL: Low density lipoprotein; PAD: Peripheral artery disease.

A calcineurin inhibitor based regimen may induce HLP independently of concurrent use of steroids[39]. Cyclosporine was shown to dose-dependently increase serum lipid concentrations. Moreover, increased total and LDL-C, along with reduced HDL-C, have been observed in patients with elevated cyclosporine blood levels[19]. Tacrolimus may have advantages over cyclosporine-based regimens in that the former does not increased serum lipid concentrations in LT recipients. Indeed, a study in which patients were switched from a cyclosporine- to a tacrolimus-based regimen found that serum LDL-C and triglyceride concentrations were reduced compared with a control group maintained on cyclosporine[40]. However, tacro-limus has been associated with hyperinsulinemia, which may result in HLP, especially hypertriglyceridemia. Both immunosuppressors have therefore been found to result in HLP in LT recipients.

The introduction of mTOR inhibitors as immuno-suppressive agents has enhanced options in the treatment of transplant recipients. Both sirolimus and everolimus are very promising mTOR inhibitors in transplant patients, but also increase the risk for development of HLP[41]. Overall all these immuno-suppressants may result in HLP, mostly hypertri-glyceridemia and combined hyperlipidemia. HLP associated with mTOR inhibitors may, however, be transient in some patients. Although mTOR inhibitors affect lipid metabolism and are therefore more likely to result in HLP, patients with pre-existing HLP still can be treated using mTOR inhibitors. These agents do not exacerbate HLP in all of these patients. Furthermore, mTOR inhibitors may enhance renal recovery, im-proving lipid status by reducing calcineurin inhibitor concentrations.

HLP IN LIVER TRANSPLANT RECIPIENTS TREATED WITH MTOR INHIBITORS

Table 3 shows recommended target serum concen-trations and upper limits of triglycerides in LT patients who receive mTOR inhibitors as immunosuppressive agents. Long-term triglyceride serum concentrations > 400 mg/dL should be avoided to prevent long term metabolic disorders such as non-alcoholic fatty liver diseases and insulin resistance. Furthermore,

triglyceride serum concentrations > 1000 mg/dL may lead to acute or chronic pancreatitis. Immunosu-ppressive regimens using mTOR inhibitors should be avoided if triglyceride serum concentrations exceed 500 mg/dL despite changes in diet and lifestyle and despite administering lipid-lowering agents. In addition, mTOR inhibitors should not be administered to LT recipients, especially those with atherosclerosis, if their serum LDL-C concentrations are > 250 mg/dL despite treatment with lipid lowering agents and lifestyle modifications. mTOR inhibitors may also result in proteinuria, aggravating any preexisting HLP. Careful patient monitoring is therefore required to determine the clinical significance of proteinuria and associated HLP.

COMBINED HLP AFTER LIVER TRANSPLANT

Liver transplant recipients with severe combined HLP, including hypercholesterolemia and hypertri-glyceridemia, should be preferentially treate for high serum LDL-C concentrations. However, if fasting serum triglyceride concentrations exceed 500 mg/dL, this condition should be treated first due to the increased risk of pancreatitis. If patients exhibit proteinuria > 1 g/d during treatment with mTOR inhibitors, these agents should be reduced or switched. HLP associated with immunosuppressants, including mTOR inhibitors, responds well to all lipid lowering interventions, inclu-ding changes in diet, weight loss in obese patients, optimization of serum glucose concentrations and modulation of diabetes mellitus, dose reduction of co-medications, modification of immunosuppressants used, and lipid lowering agents[42]. It is not yet clear whether reducing the doses of mTOR inhibitors will lower serum lipid concentrations[43].

Patients with high serum triglyceride concentrations despite lifestyle interventions should be treated, if possible, with fenofibrate or nicotinic acid. Patients with high serum LDL-C concentrations can be treated with statins[44]. Statins have been shown safe in LT recipients[45], with pravastatin or fluvastatin showing fewer interactions than other statins with cytochrome P 450 3A4 and thus a reduced risk for interactions with immunosuppressants (Table 7).

Table 7 Lipid lowering agents, their impact on lipoprotein metabolism, and potential interaction profiles[49]

Agent (daily dose)	Interactions	Comment
HMG-CoA reductase inhibitors (statins) Lovastatin (20-80 mg) Pravastatin (20-40 mg) Simvastatin (20-80 mg) Fluvastatin (20-80 mg) Atorvastatin (10-80 mg) Rosuvastatin (5-40 mg)	Lovastatin, Simvastatin, Atorvastatin are mainly catabolized *via* hepatic CYP3A4: Caution in case of use of CYP3A4-Inhibitors (*e.g.*, Itraconazole, Ketoconazole, HIV-protease-inhibitors Erythromycin, Clarithromycin, Telithromycin, Nefazodon). Caution if fibrates or nicotinic acid are simultaneously used: high risk of myopathies. Simultaneous use of calcineurin-inhibiting agents might reduce the elimination of statins: high risk of myopathies and rhabdomyolysis. Monitoring is necessary and low statin doses at the beginning are recommended. Caution with dose escalation. No interactions have been observed between Sirolimus and Atorvastatin and between Everolimus and Atorvastatin respectively Pravastatin.	Class of drugs with the highest lipid lowering effect Contraindications: (1) advanced liver diseases; (2) Rosuvastatin: simultaneous use of Cyclosporine; and (3) Statin intolerance Caution: serious interactions due to competitive inhibition of CYP450 3A4-metabolism cannot be ruled out: Prefer Fluvastatin or Pravastatin for treatment due to absence of CYP450 3A4 metabolisis.
Bile acid binding anion exchange resins Colestyramine (4-16 g) Colesevelam (2.5-3.75 g)	Caution: may reduce or retard gastrointestinal absorption of simultaneous orally administered agents. If interactions are possible, agents should be taken > 1 before or > 4 h after Colestyramine intake. Colesevelam should be taken 4 h before or after taking other drugs. Blood level monitoring is required for agents with a narrow therapeutic window. Caution with simultaneous use of immunsuppressants or lipid lowering agents. *e.g.*, bioavailability of mycophenolic acid can be reduced due to the simultaneous use of bile acid binding anion exchange resins (40% in case of MMF + Colestyramine). Intervals of medication intake mentioned above are obligatory.	Lowering of LDL-cholesterol, also used in combination with Statins or Ezetemibe Contraindications: Ileus or occlusion of bile ducts
Nicotinic acid Sustained-release tablets (Niaspan®) (1-2 g) Nicotininc acid/ Laropiprant (Tredaptive®) (1-2 g)	In some cases simultaneous use of nicotinic acid and HMG-CoA reductase inhibitors was associated with myopathies/rhabdomyolysis: careful assessment of risks and benefits is required. Tredaptive® (according to medicinal product's professional information use was only evaluated in combination with Simvastatin): small increase of AUC and Cmax of Simvastatin (probably without any clinical relevance). Hot drinks, alcohol and spicy foods may favor flush. Simultaneous use with nicotinic acid should be avoided.	Lowering of LDL and triglyceride serum concentrations Contraindications (1) advanced liver diseases; (2) acute peptic ulcer; and (3) arterial bleeding
Fibrates Gemfibrozil (2 × 600 mg) Fenofibrate (200 mg) Bezafibrate (200-600 mg)	Caution: Simultaneous treatment with HMG-CoA reductase inhibitors leads to an increased risk for myopathies and rhabdomyolysis. Statin serum concentrations can rise: no combination with statins or monitor patients closely. Combination with Calcineurin-Inhibitors and mTOR-Inhibitors leads to an increased risk for rhabdomyolysis and other side effects: monitoring is required.	Reducing triglycerides. Avoid combination with HMG-CoA reductase inhibitors. Contraindications (1) advanced liver dysfunction; and (2) severe renal impairment
Cholesterol resorption reducing agents Ezetemibe (Ezetrol®) (10 mg)	Caution: Simultaneous treatment with HMG-CoA reductase inhibitors leads to an increased risk of myopathies and rhabdomyolysis and elevation of liver enzymes: close monitoring of liver function is required. No combination with fibrates: tolerability and effectiveness were not evaluated. Combination with Fenofibrate leads to an increased risk for cholelithiasis and gall bladder diseases. Caution with the simultaneous use of Cyclosporine: AUC of Ezetemibe rises, no data concerning changes in Cyclosporine-blood levels available. No clinical effects and interactions with other immunosuppressants have been observed to date. Monitoring of immunosuppressive agents is required[50].	Lowering of LDL cholesterol: (1) advanced liver diseases; and (2) persistent elevated liver enzymes Rare interactions (no induction of CYP450 enzymes)

AUC: Area under the curve; CYP: Cytochrome P; LDL: Low density lipoprotein; HIV: Human immunodeficiency virus; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin.

GENERAL TREATMENT RECOMMENDATIONS FOR HLP IN LIVER TRANSPLANT RECIPIENTS

The evidence showing that reducing total cholesterol and LDL-C can prevent atherogenic end points is strong, based on results from multiple randomized controlled trials. Serum total cholesterol and LDL-C concentrations remain the primary targets of therapy. Integrating these findings with the ESC/EAS guidelines for life style changes suggest[11]: Reductions in serum LDL-C concentrations require dietary changes, especially reductions in dietary saturated fatty acids, which have the greatest impact on serum LDL-C concentrations. Dietary trans-fats and cholesterol should also be avoided, and dietary fiber increased. Excessive body weight should be reduced. Habitual physical activity should be increased. Serum triglyceride concentrations may be reduced by normalization of body weight, reduced alcohol intake (forbidden for LT recipients) and reduction of mono- and disaccharides, along with increased physical activity and reduced total dietary carbohydrates. Ingestion of n-3-polysaturated fats should be eliminated and replaced by mono- or polyunsaturated fats. Omega-3-fatty acids may also improve severe hypertriglyceridemia in transplant patients since no drug-drug-interactions have been described. The latter are available over the counter and are approved by the FDA for the treatment of patients with very high triglyceride serum concentrations (> 500 mg/dL)[46]. However, omega-3-fatty acids may increase serum concentrations of LDL-C and TC.

Serum HDL-C concentrations may be increased by reducing dietary trans-fats. Increased physical activity, reduced body weight and replacement of dietary carbohydrates by unsaturated fats can also increase serum HDL-C concentrations.

Depending on additional individual risk factors for cardiovascular events, in addition to LT, medical treatment of hypercholesterinemia should be considered. The ESC/EAS guidelines utilize the SCORE system to estimate the 10-year risk of a first fatal atherosclerotic event (heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death). This 10-year risk of CVD death can be estimated using tables on the ESC/EAS homepage (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Dyslipidaemias-Management-of). The current joint European Guidelines on CVD prevention in clinical practice also recommend the use of the SCORE system because it is based on large, representative European cohort data sets[47]. The 2013 ACC/AHA guidelines, which also describe the elevated risk for CVD in LT recipients CVD, recommend statin treatment. These guidelines have found a net benefit from statin treatment when 10-year atherosclerosis CVD risk was as low as 5%.

MANAGEMENT OF LIPID LOWERING AGENTS AND PHARMACOLOGICAL INTERACTIONS

If an LT recipient receiving immunosuppressive therapy has a risk profile indicating the use of lipid lowering agents such as statins, serum concentrations of creatine kinase (CK) and liver enzymes should measured one, two, four, eight and 12 wk after starting a lipid lowering treatment, as severe side effects, such as rhabdomyolysis, may occur. Subsequent blood controls may be performed every 3 mo or whenever a new drug is introduced. A tolerable elevation of creatine kinase has defined as an increase to five times the upper limit of normal on two occasions. How statins affect skeletal muscle is not clear. Myopathy often occurs in persons, such as LT recipients, taking multiple medications. Myalgia without CK elevation has been reported to occur in 5%-10% of patients. Patients taking statins should be instructed to promptly report unexpected muscle pain or weakness. However, patients complaining of myalgia without elevated serum CK concentrations can continue taking statins if their symptoms are tolerable. If the symptoms are not tolerable or are progressive, the drug should be discontinued[11].

Table 7 highlights additional important and frequently observed drug-drug interactions. Due to the high risk of rhabdomyolysis, combinations of lipid lowering agents should be avoided. Bile acid binding agents may impair the absorption of some co-medications. Therefore, comedications should be administered a least one hour before or four hours after taking bile acid binding agents[48].

CONCLUSION

HLP can include hypercholesterolemia and/or hypertriglyceridemia. High serum LDL-C is associated with the development of atherosclerosis whereas hypertriglyceridemia may have metabolic consequences. As hypertriglyceridemia originates at least partially from malnutrition and obesity, high serum triglyceride concentrations may be reduced by lifestyle modifications, which may also increase serum HDL-C concentrations. Dietary measures have little effect in reducing high serum LDL-C concentrations. Because many LT recipients are at risk for CVD, lipid lowering medication is frequently required in this patient cohort. Modification of immunosuppressive agents according to their side-effect profiles and the early initiation of statin treatment to achieve targeted serum LDL-C concentrations may have a positive impact on primary prevention of cardiovascular events in LT patients.

HLP in LT recipients may result from different etiologies, including immunosuppressive agents. Immunosuppression using mTOR inhibiting agents should be administered
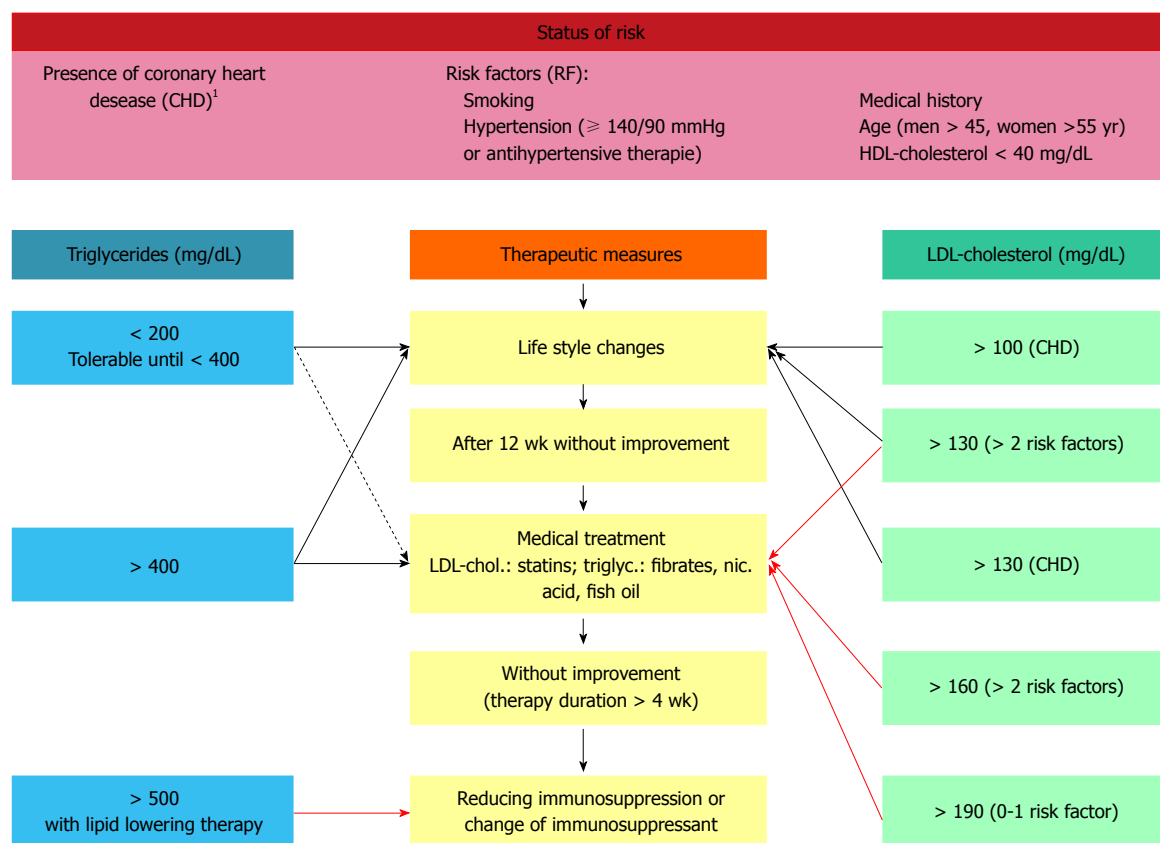
Figure 1 Algorithm for the diagnosis and treatment of hyperlipidemia in liver transplant recipients[49]. [1]Presence of cerebrovascular sclerosis or sclerosis of peripheral arteries. CHD: Coronary heart disease; LDL: Low density lipoprotein.

carefully to patients with known HLP, but should not be avoided generally. Serum lipid concentrations are not always impaired and may sometimes even improve during the use of mTOR inhibitors. LT recipients with serum triglyceride concentrations > 500 mg/dL and those with high serum LDL-C concentrations despite treatment with lipid lowering agents should not be administered mTOR inhibitors. Moreover, care should be taken in administering these pagents to patients with high serum LDL-C concentrations. mTOR inhibitors may also result in proteinuria (CAVE: nephrotic syndrome), which in turn increases serum lipid concentrations. Therefore, proteinuria should be monitored regularly in patients receiving these agents.

Patients should be regularly monitored for drug-drug interactions between lipid lowering and immuno-suppressive agents. For example, combining calcineurin inhibitors, mTOR inhibitors and statins may increase the serum concentrations of these drugs. Due to increased risk of rhabdomyolysis, combinations of lipid lowering agents should be avoided in LT recipients. HLP in LT recipients receiving immunosuppressive agents is treatable and responds well to lipid lowe-ring regimens. Transplant recipients should also be monitored for secondary causes of HLP, including hypothyroidism, diabetes and nephrotic syndrome. The latter is characterized by proteinuria exceeding 3.5 g/24 h combined with hypoalbuminemia, edema, hyperlipidemia and lipiduria. Excessive combined

hyperlipidemia, mostly type V HLP, occurs in patients with nephrotic syndrome. Therefore, treatment of nephrotic syndrome is important in LT recipients.

We recommend that fasting lipid panel (total cholesterol, LDL-C, HDL-C and triglycerides) be mea-sured in LT recipients before initiating statin therapy. Patients should be followed-up after one, two, four, eight, and 12 wk, and every three months therafter, to assess safety and efficacy. This is consistent with the ACC/AHA guidelines on the Treatment of Blood cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults[12]. Figure 1 provides an overview, based on these recommendations and our experiences in following up LT patients, on the diagnosis and possible therapeutic interventions in lipid management of LT recipients. As cardiovascular disease is the leading cause of long term mortality in LT recipients, additional prospective studies are warranted to confirm these findings and determine whether these risk-reduction strategies can attenuate the increased cardiovascular risk seen in this population.

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