Abstract

Introduction
Treatment of dyslipidaemia complicated by chronic kidney disease is important for preventing the development of cardiovascular disease. The pathogenesis of dyslipidaemia associated with chronic kidney disease varies depending on urinary protein level and the stage of chronic kidney disease. Hypocholesterolaemia is associated with malnutrition and inflammation and also leads to the poor prognosis of dialysis patients. Statins are expected to prevent the development of cardiovascular disease in non-dialysis chronic kidney disease patients; however, there is no evidence of the efficacy of statins in preventing the development of cardiovascular disease in dialysis patients. Treatment strategies for dyslipidaemia in chronic kidney disease patients mainly include life-style changes, dietary therapies and medications such as statins; care should be taken with regard to the side effects of medicines. The aim of this article is to discuss dyslipidaemia in patients with chronic kidney disease.

Conclusion
Patients who showed abnormal findings in the lipid test should be treated by considering not only their test results but also their general condition including nutritional condition, medical history and complications. Personalised treatment of each patient, rather than across-the-board treatment, is necessary.

Introduction
Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD) and must be prevented to improve their prognosis. Atherosclerosis is often a complication of CKD and adversely affects the prognosis of patients with CKD. Dyslipidaemia is a cause of atherosclerosis. The relationship between pulse wave velocity (PWV) and very low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), and low-density lipoprotein cholesterol (LDL-C) levels has been reported. The Lipid Lowering and Onset of Renal Disease (LORD) trial showed that atorvastatin suppressed the decrease in PWV. The Atherosclerosis Risk in Communities (ARIC) study showed that hypercholesterolaemia and hypertriglyceridaemia are the risk factors for CVD. Dyslipidaemia can develop at any stage of CKD and is a risk factor for CVD; hence, methods to control dyslipidaemia should be examined. This article discusses dyslipidaemia in patients with CKD and also the methods to treat these patients.

Discussion
Pathogenesis of dyslipidaemia
The pathogenesis of dyslipidaemia associated with CKD varies depending on the urinary protein level and the stage of CKD. For patients with nephrotic syndrome who have high urinary protein levels, albumin production is enhanced in the liver to compensate for hypoproteinæmia. At the same time, the synthesis of apolipoprotein (apo) B (apoB) is enhanced, resulting in elevated levels of VLDL-C and LDL-C. For patients with CKD who do not have as high urinary protein levels as those with nephrotic syndrome, dyslipidaemia is mainly caused by dysfunction in the catabolism of lipoproteins in the peripheral tissues.

Patients with CKD at stage 3 or later show abnormal levels of lipoproteins and apolipoproteins, that is, decreased levels of apoA-I, apoA-II, and apoA-IV. The level of apoC-III, an inhibitor of lipoprotein lipase (LPL), is elevated and the apoA-I/apoC-III ratio decreases. With increasing apoC-III level, the production of VLDL, which is less affected by LPL activity, is enhanced, resulting in an elevated VLDL-C level. In CKD patients with diabetes mellitus, the production of triglycerides (TGs) is also enhanced because of diabetes mellitus, which overlaps with the above-mentioned pathologies.

In dialysis patients (CKD stage 5D), LPL activity decreases because of the accumulation of uremic toxins and secondary hyperparathyroidism. Because hepatic triglyceride lipase activity also decreases, the conversion of IDLs to LDLs becomes difficult, resulting in elevated IDL levels and decreased LDL levels. The increase in IDL level leads to an increase in TG level. Although LDL level decreases, its plasma residence time increases, leading to degeneration caused by oxidation and accelerating atherosclerosis. Haemodialysis patients may have hypertriglyceridaemia and hypo-high-density lipoproteinemia.
lipoprotein (HDL) cholesterolemia. The levels of small-dense LDLs and lipoprotein(a) \([\text{Lp(a)}]\) are elevated, resulting in a decrease in the levels of apoA-I and apoA-II and an increase in the levels of apoB, apoC-III, and apoE. Although heparin used during dialysis has been considered to decrease LPL activity, the decrease in LPL level in blood plasma after the treatment with heparin is not statistically significant, indicating that the use of heparin does not strongly affect lipid metabolism. In peritoneal dialysis, the loss of protein and the absorption of glucose from the peritoneal dialysis solution occur, resulting in a larger elevation of the levels of total cholesterol, IDL-C, LDL-C, and Lp(a) than in haemodialysis. In peritoneal dialysis, the apoB level is elevated. The small-dense LDL level is also elevated by the decreased clearance of VLDL.

**CKD progression**

Dyslipidaemia is a risk factor for CKD progression. In an observational study of patients undergoing medical check-up in local communities, hypercholesterolaemia and hypertriglyceridaemia are the risk factors for CKD progression. There have been many reports on the protective effect of statins on kidney functions. As statins have been reported to decrease urinary protein level, a meta-analysis of 15 studies demonstrated that the urinary albumin level decreased by 47% in patients with a urinary albumin level of at least 300 mg/dL. In a meta-analysis of six studies, statins decreased urinary protein level. A subgroup analysis of a Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study and LIVALO Effectiveness and Safety (LIVES) study revealed that statin treatment improved the estimated glomerular filtration rate (eGFR). However, in the Study of Heart and Renal Protection (SHARP), no significant differences in the progression of end-stage renal disease were observed between the groups with and without statin treatment. In a meta-analysis of 11 studies, statins did not improve eGFR. Prospective studies of the outcome of the treatment with statins in terms of preventing the progression of kidney dysfunction are expected.

**Cholesterol paradox**

Although dyslipidaemia is a cause of atherosclerosis and a risk factor for CVD, previous studies of dialysis patients showed that the risk of mortality increases with decreasing total cholesterol level. This is called the cholesterol paradox. Moreover, studies also showed that the risk of mortality in dialysis patients without malnutrition or inflammation increases as total cholesterol level increases. Decreased cholesterol levels may reflect malnutrition and chronic inflammation and increase the risk of mortality in dialysis patients with malnutrition and inflammation. To improve the prognosis of such dialysis patients, it is necessary to control atherosclerosis caused by dyslipidaemia and to maintain their good nutritional state.

**Target cholesterol level**

From the finding that dyslipidaemia is a risk factor for CVD, Kidney Disease Outcomes Quality Initiative guidelines recommend that the target LDL-C level in patients with CKD be lower than 100 mg/dL. Although the lower limit of the target LDL-C level is not specified, a lower LDL-C level is considered to be better because Treating to New Targets (TNT) study revealed that CVD development is suppressed in patients with a target LDL-C level of 70 mg/dL. However, considering the cholesterol paradox, it is unclear whether strictly following this guideline of lowering LDL-C level is beneficial for all patients. Dyslipidaemia of patients with malnutrition should be treated after malnutrition has been improved. Moreover, target lipid levels may differ between patients with and without malnutrition, requiring evidence under different conditions.

**Treatment**

Treatment of dyslipidaemia should start with lifestyle changes. This includes education about smoking cessation. In dietary therapies, a low-protein diet for CKD should be designed in addition to the restriction of total energy and fat intake. Appropriate exercise therapy should be provided depending on the physical ability of individuals. Medications should be taken only when cholesterol remains high despite lifestyle changes.

**CVD suppression by statins in patients with CKD**

In a meta-analysis of 26 studies of patients with CKD stages 3–4, statins reduced the risk of mortality, risk of fatal CVD and risk of nonfatal CVD. A subgroup analysis in the TNT study and the MEGA study indicated that statins decrease CVD risk and total mortality in patients with CKD.

Intervention trials using statins in haemodialysis patients include the Die Deutsche Diabetes Dialyse Study (4D Study), A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) and SHARP. In the 4D study of patients with type 2 diabetes mellitus, atorvastatin statistically significantly reduced the risk of cardiac events by 18%. However, the risk of stroke increased. There were no significant differences in the risk of these end points in patients with an LDL-C level of 145 mg/dL or lower. In the AURORA study of dialysis patients in a randomised trial of rosuvastatin, there were no significant differences in the risk of the composite end point (cardiovascular death, nonfatal myocardial infarction or brain infarction). In SHARP study of non-dialysis CKD patients...
Critical review

Medications for dyslipidaemia

There are eight patterns of dyslipidaemia (Figure 1). Considering these patterns, medications should be selected. On the basis of efficacy and evidence of medications, statins are considered the first option of medication (Table 1). Almost all statins are metabolised by the liver and can be basically used at a typical dose even in patients with deteriorated kidney function. Ezetimibe is excreted with the bile and can be used with other drugs including statins. Sevelamer, although not a lipid-lowering drug, can be used to improve hyperphosphataemia in dialysis patients; it decreases LDL-C level and increases HDL-C level. Fibrates are excreted by the kidney and tend to have side effects in patients with an advanced stage of CKD, and the combined use of fibrates and statins requires great care. Probucol is excreted with the bile but often has side effects, namely digestive symptoms such as diarrhoea and sometimes irregular heartbeat, requiring medical attention.

When lowering LDL-C level using statin is not enough, combination regimens are needed to reach lipid targets. Even in patients with normal LDL-C levels, combination therapies are required for the control of other lipid abnormalities.

Table 1 Lipid lowering medications and estimated changes in lipid levels

<table>
<thead>
<tr>
<th>Medication</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Strongly decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Moderately decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Probucol</td>
<td>Decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Moderately decrease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrate</td>
<td>Decrease</td>
<td>Increase</td>
<td>Strongly decrease</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Decrease</td>
<td>Increase</td>
<td>Strongly decrease</td>
</tr>
<tr>
<td>Eicosapentaenoic acid</td>
<td></td>
<td></td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Decrease, decreases lipid levels; HDL-C, high-density lipoprotein cholesterol; increase, increases lipid levels; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Figure 1: Treatment patterns of dyslipidaemia.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
goals. Although no second option (i.e. when statins are inapplicable or ineffective) is specified, ezetimibe and bile acid sequestrants have complementary effects that suggest they may be appropriate for use in combination with a statin (Table 2). Statin and ezetimibe combination therapy shows an additional 12%–21% LDL-C level reduction. A systematic review showed that adding colestipol or cholestyramine to a statin provides an additional 7%–20% LDL-C level reduction. Combinations of statins with fibrates can treat combined dyslipidaemia by decreasing LDL-C level more than 40%, decreasing TG levels over 50% and increasing HDL-C levels more than 20%.

Conclusion
In this article, we describe the pathogenesis of dyslipidaemia in patients with CKD, the association of dyslipidaemia with cholesterol, atherosclerosis, the prognosis of patients with CKD, and the treatment of dyslipidaemia. Treatment of dyslipidaemia complicated by CKD is important to prevent the development of CVD and the progression of kidney dysfunction. Because there is a wide range of characteristics of patients with CKD, personalised treatment of each patient, rather than across-the-board treatment, is necessary.

Abbreviations list
4D Study, Die Deutsche Diabetes Dialyse Study; apoB, apolipoprotein B; ARIC, Atherosclerosis Risk in Communities; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis; An Assessment of Survival and Cardiovascular Events; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IDL-C, intermediate-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LIVES, LIVALO Effectiveness and Safety; LORD, Lipid lowering and Onset of Renal Disease; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PWV, pulse wave velocity; SHARP, Study of Heart and Renal Protection; TG, triglyceride; TNT, Treating to New Targets; VLDL-C, very low-density lipoprotein cholesterol.

References

Table 2 Combination therapies with statin and estimated changes in lipid levels

<table>
<thead>
<tr>
<th>Combination</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>Strongly decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Strongly decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Fibrate</td>
<td>Strongly decrease</td>
<td>Increase</td>
<td>Strongly decrease</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Strongly decrease</td>
<td>Increase</td>
<td>Strongly decrease</td>
</tr>
</tbody>
</table>
| **Decrease, decreases lipid levels**; HDL-C, high-density lipoprotein cholesterol; increase, increases lipid levels; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.