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PREFACE

The kidney and lipids: preface

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Introduction

From June 5 through June 7, 2013, there was a World Congress of Nephrology 2013 Satellite Symposium on the Kidney and Lipids in Fukuoka, Japan. This meeting was held in conjunction with The 25th Annual Meeting of Japanese Society of Kidney and Lipids. There were 158 participants, all with an interest in the role of lipid abnormalities in chronic kidney disease (CKD).

There is a long history of speculation regarding the association between lipid abnormalities and CKD. Virchow [1] was one of the first to describe this association and referred to the "fatty metamorphosis" of diseased kidneys as early as 1860. Fifty years later, Munk was intrigued by fatty deposition in patients with nephrotic syndrome and coined the term "Lipoidnephrose" [2]. Others subsequently referred to the presence of lipid in diseased kidneys and speculated on its role in the pathogenesis of kidney damage. Kimmelstiel and Wilson [3] in their classic description of diabetic nephropathy in 1936 noted the prominent role of lipid deposition.

More recently, attention was again focused on the possible role of lipids in CKD with the publication of an editorial review by Moorhead et al. [4] in 1982. They hypothesized that lipid abnormalities might be both a consequence and a cause of progressive kidney injury. Specifically, lipids might be involved in glomerular and tubular injury in much the same way that dyslipidemia causes atherosclerosis. A number of groups actively investigated ways to test this hypothesis and in October 8–10, 1998, there was a symposium on "Lipids and Renal Disease" at Kashikojima/Ise-Shima National Park, Japan [5]. Since that time, there have been many more basic science studies and clinical trials testing the hypothesis that dyslipidemia may play an important role in the development and progression of CKD. Thus, the organizers thought it was an opportune time to gather and discuss what we know, and what we need to learn regarding this important topic. This preface reviews a few of the highlights of the meeting, many of which are described in more detail in the articles of this special issue.

Clues to the pathogenesis of lipid-induced kidney injury

Lipid deposition

There are a number of mechanisms whereby CKD causes abnormalities in lipids, and these abnormalities may in turn cause renal injury (Fig. 1). Certainly, abnormalities in circulating lipoproteins can cause lipid deposition and glomerular damage. Patients with lecithin:cholesterol acyltransferase (LCAT) deficiency, a rare genetic disorder, have high circulating free cholesterol and phospholipid concentrations, and develop lipid deposition in renal glomeruli that leads to chronic progressive kidney disease. Strong evidence that the renal damage in LCAT deficiency is from abnormalities in circulating lipoproteins has come from observations of disease recurrence in transplant recipients [6]. Of interest, a temporary appearance of anti-LCAT antibody in membranous nephropathy can lead to

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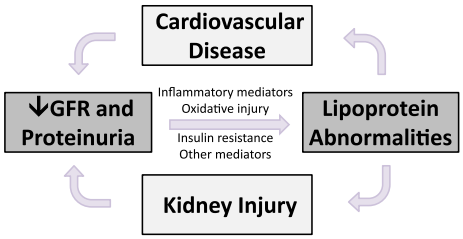

Fig. 1 Possible mechanisms explaining the association between dyslipidemia and CKD progression

glomerular lesions similar to those in familial LCAT deficiency [7]. However, the classic proof-in-concept demonstration that abnormalities in circulating lipoproteins may cause progressive kidney damage has been provided by studies of Lipoprotein Glomerulopathy (LPG) [8]. Patients with LPG have a marked increase in serum apolipoprotein E (ApoE) concentrations. Several novel ApoE mutations are associated with LPG. One of them, ApoE Sendai, has been shown to cause LPG when transduced in ApoE-deficient mice [9].

Role of lipids in diabetic nephropathy

Can abnormalities in circulating lipoproteins be involved in more common types of progressive kidney disease, such as diabetes mellitus? A recent meta-analysis examined associations between genetic variants and diabetic nephropathy, defined as proteinuria or end-stage renal disease [10]. There were 34 genetic variants that were each replicated in more than one study, and of these, 21 remained significantly associated with diabetic nephropathy in a random-effects meta-analysis. Interestingly, the strongest association was with the ApoE genetic variants. Specifically, in 11 studies ($N = 2812$ subjects) the odds ratio for ApoE E2 was 1.70 (95 % CI 1.12–2.58), with greater than 1.00 indicating greater odds of diabetic nephropathy. The odds ratio for ApoE E4 was 0.78 (95 % CI 0.62–0.98), with less than 1.00 indicating reduced odds of diabetic nephropathy. While these results are far from conclusive, they do support the hypothesis that ApoE abnormalities could be a risk factor for diabetic nephropathy and/or its progression. It may not be a coincidence that the ApoE genetic variants were associated with diabetic nephropathy, given the evidence of a role for ApoE in other kidney diseases.

Apolipoprotein L1 nephropathy

Apolipoprotein L1 (APOL1) gene variants confer resistance to *Trypanosoma brucei rhodesiense* (the cause of sleeping sickness). APOL1 gene variants are also strongly associated with CKD in African Americans, including hypertensive nephrosclerosis, focal segmental glomerulosclerosis, and human immunodeficiency virus nephropathy [11, 12]. Understanding the mechanisms for these associations is an intense area of investigation. Theories include the "two hit" hypothesis and a possible role of cellular autophagic pathways. Is the fact that the genetic abnormality involves an apolipoprotein gene providing a clue, or is this due to linkage disequilibrium or other non-lipoprotein mechanisms. Some observational data suggest differences in HDL particles [13]. Clearly, additional studies will be forth coming, and unraveling this association will likely provide important pathogenic information regarding the pathogenesis of progressive renal disease.

Treatment

Low-density lipoprotein apheresis

It has long been noted that LDL apheresis can cause a marked and immediate diminution in proteinuria in steroid-resistant nephrotic syndrome [14]. Recent long-term follow-up suggests that the effect can be sustained for several years, at least in some patients [15]. Additional studies will be important to better understand the mechanism(s).

Statins and cardiovascular disease in CKD

A number of multi-center, randomized controlled trials (RCTs) investigating the effects of 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitors (also known as statins) on cardiovascular disease have included patients with CKD. In addition, there are now also RCTs of statins in patients with CKD.

The Assessment of LEscol in Renal Transplantation was a double-blind RCT of fluvastatin in 2102 kidney transplant recipients with serum cholesterol 4.0–9.0 mmol/L at least 6 months after transplantation [16]. The primary endpoint, major adverse cardiac events (MACE), was not significantly different ($P = 0.139$) between the two groups, but important secondary endpoints were better with fluvastatin. In addition, after longer follow-up, the differences in MACE were statistically significant [17].

Interestingly, Die Deutsche Diabetes Dialyse (4-D) Studie [18], and the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [19], both failed to produce reductions in MACE. A number of explanations have been given for these surprising results, including the possibility that many MACE were not atherosclerotic.

The Study of Heart and Renal Protection enrolled 9270 patients with CKD (3023 on dialysis and 6247 not on dialysis) with no known history of myocardial infarction or coronary revascularization [20]. The primary endpoint, MACE, was

reduced by treatment with simvastatin 20 mg combined with ezetimibe 10 mg. Interestingly, in a subgroup analysis, there was no difference in MACE among dialysis patients. Also notable was the fact that pre-specified endpoints of CKD progression among those not on dialysis at enrollment were not significantly different between the two groups.

In light of the several RCTs of statins in patients with CKD, at least two meta-analyses have been conducted [21, 22]. Although the two meta-analyses differed in design and in which studies were included, their results were very similar. They concluded that statins reduce the risk of CVD and all-cause mortality in CKD Stage 3–5, that evidence for benefit in dialysis patients is lacking, and that evidence for benefit after transplant is sparse. There was some evidence that statins may slow the progression of CKD, but this evidence was not conclusive.

Guidelines for treatment of dyslipidemia in CKD

Since there is now a substantial body of evidence from intervention trials in CKD, the Kidney Disease Global Outcomes (KDIGO) group convened an evidence review team and guideline work group to develop a clinical practice guideline [23]. The work group has produced a guideline that suggests treating CKD patients (not on dialysis) who are at risk for cardiovascular disease with a statin. Patients on dialysis need not start a statin, but they may continue to receive a statin if they were taking a statin before dialysis initiation.

Summary

This conference demonstrated that studying the relationship between lipid abnormalities and outcomes in patients with CKD remains a fruitful area of study. Clearly, additional studies are needed in both basic sciences mechanisms of injury, genetics and clinical trials.

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Photographs of the Symposium

1. Dr. Keane chaired the opening and touched the Japanese tradition regarding lipids and the kidney.
2. Dr. Kasiske gave the keynote address of the kidney and lipids at the opening.
3. Dr. Hirashio presented gene abnormality of LCAT deficiency.
4. Dr. Hiromura presented autoantibody of LCAT and received the Poster Session Award.
5. Dr. Saito chaired the session of LPG with Dr. Atkins and reviewed topics of LPG.
6. Dr. Stratikos presented APOE mutations in LPG.
7. Dr. Ito presented FcRγ deficiency in animal LPG and received the Poster Session Award.
8. Dr. Mooyaart presented genetic association in diabetic nephropathy.
9. Dr. O'Toole presented the APOL1 associations with kidney disease.
10. Dr. Muso presented the effect of LDL apheresis in nephrotic syndrome.
11. Dr. Holdaas presented results of the ALLERT trial.
12. Dr. Fellström presented results of AURORA study.
13. Dr. Upadhyay presented meta-analysis of statins in CKD.
14. Dr. Wanner chaired the session of lipid-lowering treatment in CKD with Dr. Shoji, presented results of the 4D study and summarized KDIGO guideline.
15. Participants in the final session.


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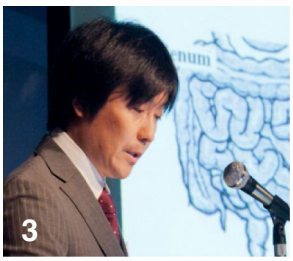
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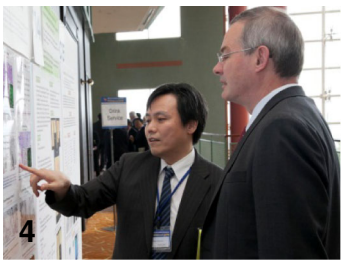
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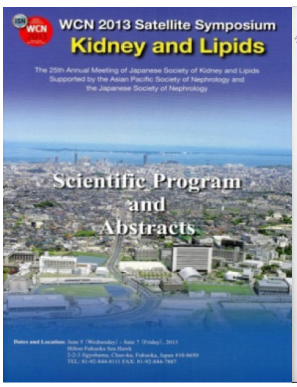

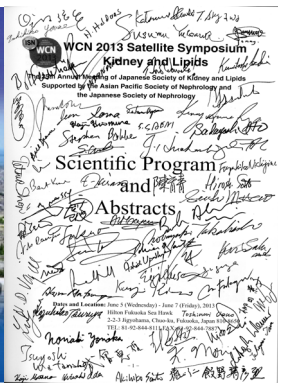


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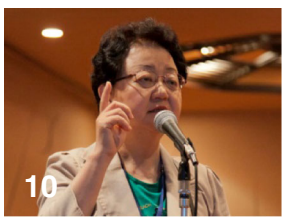
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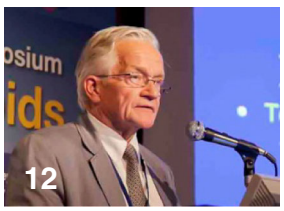
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