Review

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Current Focuses in Serum Lipid Abnormalities in Dialysis Patients

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Dyslipidemia · Clinical practice guideline · Omega-3 polyunsaturated fatty acids · Cholesterol absorption · Dysfunctional high-density lipoproteins

Abstract
Background: Dyslipidemia is a common metabolic complication in patients with chronic kidney disease and is detected as changes in lipoprotein concentrations in serum. ***Summary:*** Recently, other features of lipid abnormalities have been described, such as alterations in serum n–3 polyunsaturated fatty acids, cholesterol metabolism (proportion of hepatic synthesis and intestinal absorption), and dysfunctional high-density lipoprotein. ***Key Messages:*** Since abnormalities of these new aspects predict adverse outcomes in hemodialysis populations, they may be helpful in risk stratification of patients and could also be new targets for prevention.

Introduction

Patients with chronic kidney disease (CKD), particularly those treated with hemodialysis, have increased risk of cardiovascular disease (CVD). Dyslipidemia is often seen in CKD and is an important risk factor for atherosclerosis and atherosclerotic CVD in CKD [1].

Lipid abnormalities are usually evaluated by examining the increase or decrease of the individual concentration of lipoproteins, and we understand such changes as the result of altered metabolism of lipoproteins. For example, hepatic secretion of very low-density lipoproteins is increased in those with heavy proteinuria. In contrast, patients with renal failure have impaired catabolism of very low-density lipoproteins in peripheral tissue, and also accumulation of intermediate-density lipoproteins occurs because of the decreased level of hepatic triglyceride lipase. The diagnosis of dyslipidemia and many clinical practice guidelines for the management of dyslipidemia are based on the level of serum lipids and lipoproteins.

However, it has become clearer that some abnormalities in serum lipids and lipoproteins are difficult to detect by a routine lipid panel, but may be closely associated with the increased risk of CVD in those with CKD. In this article, we review three topics: the serum n–3 polyunsaturated fatty acids (PUFA) profile, cholesterol metabolism (hepatic synthesis and intestinal absorption), and dysfunctional high-density lipoprotein (HDL).

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Alterations in the Serum PUFA Profile in CKD and Its Association with CVD

What Are PUFAs?

Lipoproteins consist of proteins called apolipoproteins and lipids such as phospholipids and unesterified cholesterol on the surface and triglycerides and esterified cholesterol located in the core of lipoproteins. One molecule of esterified cholesterol has one molecule of fatty acid bound by ester bond, and phospholipids and triglycerides have two and three molecules of fatty acids per molecule, respectively. The non-esterified form of fatty acids is called non-esterified fatty acids or free fatty acids, and they are bound to albumin in the circulation. Differences in fatty acids in cell membrane phospholipids could affect physicochemical and biological properties of cell membranes and cellular activities.

Fatty acids are classified, by the number of unsaturated bonds (double bonds) in their carbon chains, into saturated fatty acids, monounsaturated fatty acids, and PUFAs. The latter are further classified into n–3 (ω3) and n–6 (ω6) PUFAs by the location of the unsaturated bonds [2]. PUFAs in cell membranes are metabolized by cyclooxygenase that produces prostaglandins or by lipoxygenase that generates leukotrienes, known as lipid mediators related to inflammation. These lipid mediators derived from arachidonic acid (AA, n–6) are generally inflammatory, whereas those from eicosapentaenoic acid (EPA), an n–3 PUFA, are less inflammatory or anti-inflammatory. Docosahexaenoic acid (DHA), another n–3 PUFA, is also the precursor of anti-inflammatory lipid mediators, such as resolvin and protectin. Therefore, the balance between n–3 PUFAs and AA is a potential regulator of inflammatory processes possibly affecting CVD risk.

Many epidemiologic studies revealed that EPA and DHA, which are abundant in fish oil, are inversely associated with risk of CVD in the general population. In addition, randomized controlled trials (RCTs) provide evidence that administration of EPA [3], alone or in combination with DHA, reduces the risk of CVD in Japan and in European countries, respectively. It is of note that replacement of saturated fatty acid with n–6 PUFA linoleic acid increased the risk of all-cause and cardiovascular mortality in an RCT in subjects with coronary heart disease [4].

Recent Findings on PUFAs in CKD

A recent study has shown that the serum PUFA profile was altered and that it predicted CVD risk in patients on hemodialysis [5]. Compared with healthy control subjects, hemodialysis patients showed lower values in EPA/AA, DHA/AA, and (EPA+DHA)/AA ratios in serum. Within the hemodialysis cohort, the risk of CVD events during the 5-year follow-up in patients in the lowest (EPA+DHA)/AA ratio quartile was 2-fold greater than those in the highest quartile.

At present, the mechanisms by which serum n–3 PUFA/AA ratios become lower in hemodialysis patients are unclear. It may be attributable to dietary changes. It is possible that dialysis patients are more likely to choose meat than fish within the limited range of dietary protein restriction. Another explanation would be some dysregulation of intrinsic fatty acid metabolism caused by uremia. Patients with type 2 diabetes mellitus have a serum PUFA profile similar to that of hemodialysis patients, and they are known to show a higher ratio of AA to dihomo-γ-linoleic acid (DGLA) ratio in serum [6]. Since DGLA is the direct precursor of AA in the metabolic pathway of n–6 PUFA, and since this step is catalyzed by an enzyme called delta5-desaturase (D5D), such an increase in the serum AA/DGLA ratio (D5D index) suggests activation of D5D in patients with type 2 diabetes mellitus. It should be examined whether or not patients with end-stage renal disease have a similar abnormality of intrinsic PUFA metabolism.

At least two RCTs have examined PUFA supplementation in CKD. First, the FISH trial examined the efficacy of fish oil supplementation (4 g per day) on graft patency in hemodialysis patients with new synthetic arterio-venous grafts for hemodialysis [7]. The primary endpoint was the proportion of participants experiencing graft thrombosis or radiological or surgical intervention during 12 months of follow-up. Compared with participants on placebo, a lower proportion of hemodialysis patients taking fish oil reached the primary endpoint but without statistical significance ($p = 0.06$). However, fish oil supplementation was effective in prolonging the time taken to reach the same endpoint ($p < 0.001$). The second trial compared the risk of the composite primary endpoint of CVD plus all-cause death during 2 years of follow-up in 206 hemodialysis patients, who were randomly allocated to treatment with either n–3 PUFAs (1.7 g/day) or olive oil (control group) [8]. There was no significant difference in the primary endpoint, although the risk of myocardial infarction was almost halved in those treated with n–3 PUFAs.

Possible Influence on Clinical Practice

Measurement of the serum PUFA profile, composed of the 4 PUFAs of EPA, DHA, DGLA and AA, can be undertaken using the health insurance system in Japan,

so it is possible for clinicians to examine the serum PUFA profile in the risk stratification of dialysis patients. In addition, treatment with n–3 PUFAs may be a possible intervention in hemodialysis patients, among whom the benefit of treatment with a statin had not been shown. However, we do not recommend such treatment with n–3 PUFAs for dialysis patients because of the lack of high-level evidence. Currently, it would be acceptable to use the PUFA profile in providing dietary advice to eat more fish, or in the treatment of patients with n–3 PUFA for the management of hypertriglyceridemia.

Changes in Cholesterol Metabolism in CKD and Its Relation to CVD

Background Knowledge About Cholesterol

The amount of cholesterol molecules in the body are the sum of cholesterol that is biosynthesized within the body (mostly in the liver) and cholesterol that is absorbed in the intestine, and these cholesterol molecules are degraded into bile acid. The rate-limiting enzyme in the cholesterol biosynthesis starting from acetyl-CoA is HMG-CoA reductase, which is the target of statins. Intestinal cholesterol absorption is mediated by the transporter Nieman-Pick C1-like protein 1 (NPC1L1), which is the target of ezetimibe. Cholesterol-7α-hydroxylase (CYP7A1) is the enzyme that degrades cholesterol into bile. Bile acid sequestrants bind to bile acids in the intestine and excrete them in the feces, resulting in reduction of the hepatic content of bile acids, up-regulation of CYP7A1, increased degradation of cholesterol to bile acid, decreased hepatic content of cholesterol, up-regulation of low-density lipoprotein (LDL) receptor expression, and finally reduction of the serum LDL cholesterol (LDL-C) level. Since CYP7A1 is present mostly in the liver, excessive cholesterol in the peripheral tissues needs to be transferred to the liver via the reverse cholesterol transport system mediated by HDL.

Serum markers have been utilized to estimate cholesterol synthesis and cholesterol absorption in the body. Since lathosterol is the precursor of cholesterol, its serum level should reflect cholesterol synthesis. The intestinal cholesterol transporter NPC1L1 also mediates the transport of plant sterols such as campesterol and sitosterol, and the concentrations of these plant sterols or other related molecules would provide indirect estimation of cholesterol absorption via the intestine. Some researchers directly use the concentrations of these markers of cholesterol metabolism in their studies, while others prefer to use the proportion of the markers to total cholesterol in serum.

It was reported that intestinal cholesterol absorption is increased in patients treated with a statin to compensate for the decrease in hepatic cholesterol synthesis. Also, among subjects with comparable serum LDL-C, high cholesterol absorbers were reported to be at an increased risk of CVD compared with low cholesterol absorbers.

Recent Findings on Cholesterol Metabolism in CKD

Two studies reported that hemodialysis patients have increased levels of cholesterol absorption markers and decreased levels of cholesterol synthesis [9, 10]. Importantly, high cholesterol absorbers were shown to have significantly higher risk of all-cause mortality [9]. These changes in cholesterol metabolism in hemodialysis patients do not appear to be attributable to hemodialysis treatment, since the increased absorption and decreased synthesis of cholesterol were reported to occur in predialysis CKD patients. In a cross-sectional study of type 2 diabetes mellitus patients, estimated glomerular filtration rate (eGFR) was positively correlated with serum lathosterol concentration but inversely correlated with serum campesterol level [11].

The underlying mechanisms by which cholesterol absorption and synthesis are modulated in those with decreased renal function are unknown. However, since NPC1L1 is suppressed by PPAR-α [12], and PPAR-α gene expression is down-regulated in uremia [13], it is reasonable to speculate that uremia suppresses PPAR-α, resulting in NPCIL1 up-regulation and increased intestinal cholesterol absorption. Following increased intestinal cholesterol absorption, hepatic cholesterol synthesis could be decreased; increased cholesterol content in chylomicron and its remnant result in increased flux of cholesterol to the liver, increased hepatic cholesterol content, and finally down-regulation of the expression of HMG-CoA reductase, a rate-limiting enzyme of cholesterol biosynthesis. Additionally, hepatic cholesterol synthesis could be suppressed in the presence of malnutrition or wasting associated with renal failure.

Possible Influence on Clinical Practice

These markers of cholesterol synthesis and absorption may be helpful to identify or stratify patients at higher risk of death and other adverse clinical outcomes. In Japan, however, these markers are not available in routine clinical practice.

The above observational studies showed that higher cholesterol absorption was an independent predictor of all-cause mortality. However, it is premature to administer ezetimibe alone to hemodialysis patients to improve clinical outcomes, since there is no direct evidence supporting ezetimibe monotherapy at present. SHARP is a large RCT that examined the effect of simvastatin plus ezetimibe versus placebo on the risk of atherosclerotic CVD in CKD patients in the predialysis and dialysis stages of treatment [14]. SHARP did not examine the effect of ezetimibe alone. In the recently published IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) [15], the effect of ezetimibe when added to a statin was tested in patients with acute coronary disease, not in those with CKD as the target population.

Clinical practice guidelines on lipid management in Japan recommend lowering LDL-C or non-HDL-C levels below 120 mg/dl or 150 mg/dl, respectively, with lipid-lowering medication such as a statin if needed [16–18]. In contrast, the KDIGO lipid guidelines recommend pharmacological treatment with a statin alone or the statin/ezetimibe combination in adults aged >50 years with eGFR <60 ml/min/1.73 m^2 but who are not treated with chronic dialysis or kidney transplantation [19]. The KDIGO guidelines also suggest that statins or the statin/ezetimibe combination should not be initiated in adults with dialysis-dependent CKD.

Dysfunctional HDL and Mortality Risk in CKD

Functions and Dysfunctions of HDL

Epidemiologic studies have shown that elevated levels of LDL-C and HDL-C are independent predictors of a high risk and a low risk of CVD, respectively. Therefore, LDL-C is called 'bad cholesterol', whereas HDL-C is called 'good cholesterol'. In addition to HDL's role in the reverse cholesterol transport system, HDL exerts its beneficial functions via its anti-oxidative and anti-inflammatory properties.

Regarding the anti-oxidative and anti-inflammatory properties of HDL, HDL possesses various active proteins on its surface such as paraoxonase 1 and platelet-activating factor-acetylhydrolase. In inflammatory conditions, HDL may consume and lose these protective factors, and at the same time, pro-inflammatory substances may accumulate on the surface of HDL, such as serum amyloid A (SAA), apo J, and secretory phospholipase A2. Such alterations in surface components are believed to make HDL particles into less anti-atherogenic or rather pro-atherogenic particles. The presence of such HDL has been detected in CKD and other disease states, and these HDL particles are called 'inflammatory HDL' or 'dysfunctional HDL' [20].

Recent Findings in CKD

Dysfunctional HDL found in CKD is also called 'uremic HDL' or 'HDLckd'. According to an epidemiologic study by Kalantar-Zadeh et al. [21], hemodialysis patients with inflammatory HDL had a higher risk of all-cause mortality than those without inflammatory HDL. Honda et al. [22] measured the plasma concentration of oxidized HDL and showed that the plasma oxidized HDL level was higher in those with protein-energy wasting or inflammation. Also, a higher plasma oxidized HDL level was an independent predictor of CVD. Kopecky et al. [23] measured plasma concentrations of HDL which had SAA or surfactant protein B on its surface in the participants of the 4D trial, and found that hemodialysis patients having high concentration of SAA-bound HDL showed a higher risk of CVD, and that those with a higher concentration of surfactant protein B-bound HDL had an increased risk of all-cause mortality. Moradi et al. [24] reported a U-shaped association between HDL-C and CVD mortality rate in a cohort of dialysis patients in the US, and discussed the possibility of increased dysfunctional HDL as the explanation for the U-shaped relationship in the hemodialysis population.

Possible Influence on Clinical Practice

The assays for oxidized HDL, SAA-bound HDL, and others are available only for research purposes and not yet for clinical chemistry. Regarding the use of usual HDL-C measurement in the CVD risk assessment of dialysis patients, reports from Western countries provide negative results. In contrast, in a large observational cohort study from Japan (N = 45,390) [25], the risk of incident myocardial infarction was higher in hemodialysis patients having lower HDL-C, as well as in those having higher non-HDL-C levels. Thus, epidemiology regarding dyslipidemia and CVD among hemodialysis patients appears to be quite different between Japan and Western countries. This difference possibly derives from background inflammatory status. The median C-reactive protein level of hemodialysis patients was 0.1 mg/dl in the above report from Japan, which is much lower than that of such patients in Western countries. Thus, it is my opinion that the usual measurement of HDL-C can be used for CVD risk prediction in Japanese hemodialysis patients with less inflammatory states.

Conclusions

This article provided a summary of three recent topics in lipid abnormalities in CKD and dialysis patients. The term 'lipid metabolism' is often used, but we only measure the level of certain components of lipoproteins in routine clinical practice. We would understand more if we consider the conversions of lipoproteins, the dynamic flow of their components, and possible alterations in their functionality. Further studies are needed in order to utilize the new findings in daily clinical practice for better management of lipid abnormalities in CKD and dialysis patients.

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Conflicts of Interest

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