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ApoB and apoM – New aspects of lipoprotein biology in uremia-induced atherosclerosis

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ABSTRACT

Chronic kidney disease affects as much as 13% of the population, and is associated with a markedly increased risk of developing cardiovascular disease. One of the underlying reasons is accelerated development of atherosclerosis. This can be ascribed both to increased occurrence of traditional cardiovascular risk factors, and to risk factors that may be unique to patients with chronic kidney disease. The latter is reflected in the observation that the current treatment modalities, mainly directed against traditional risk factors, are insufficient to prevent cardiovascular disease in the patient with chronic kidney disease. This review discusses mechanisms accelerating uremic atherosclerosis with a specific focus on the putative roles of apolipoprotein(apo)s B and M that may be particularly important in patients with chronic kidney disease.

1. Introduction

Chronic kidney disease is characterized by progressive loss of kidney function. Defective kidney clearance causes accumulation of metabolic waste products in the blood, *i.e.* uremia (Levey et al., 2012). Chronic kidney disease affects ~13% of the population and the prevalence is rising (Hill et al., 2016; Eckardt et al., 2013). Hence, chronic kidney disease does not merely affect the health of individuals, but also poses a growing economic burden for society (Jha et al., 2013; Levey et al., 2012; Hill et al., 2016). At early stages, the disease is often asymptomatic, but continued progression leads to end-stage renal disease, where dialysis or transplantation is needed (Levey et al., 2012). Remarkably, cardiovascular disease-related death is a more likely outcome than progression to end-stage renal disease in all stages of chronic kidney disease (Gansevoort et al., 2013). Thus, patients with chronic kidney disease have a markedly increased risk of dying from cardiovascular disease (Vanholder et al., 2005).

1.1. Chronic kidney disease – a progressive disease accelerating atherosclerosis

Chronic kidney disease is a progressive disease. Irrespective of etiology, chronic kidney disease is often characterized by inflammation-driven fibrosis in the kidney (Vega et al., 2016; Mutsaers et al., 2015). Disease severity in patients with chronic kidney disease is graded according to kidney function judged by the glomerular filtration rate (GFR): Stage 1: Normal GFR (GFR≥90 ml/min/1.73 m^2); Stage 2: Mild reduction in GFR (GFR 60–89 ml/min/1.73 m^2); Stage 3: Moderate reduction in GFR (30–59 ml/min/1.73 m^2); Stage 4: Severe reduction in GFR (15–29 ml/min/1.73 m^2); Stage 5: End-stage renal disease, where GFR is < 15 ml/min/1.73 m^2 or permanent kidney replacement therapy (*i.e.* dialysis or transplantation) has been initiated (Webster et al., 2016). Even when kidney dysfunction is mild, as in chronic kidney disease Stage 2, there is an inverse correlation between GFR and risk of cardiovascular disease. Hence, the threshold for increased risk of cardiovascular disease is likely as high as 75 ml/min/1.73 m^2 (Gansevoort et al., 2013). Thus, the chronic kidney disease patient group has one of the highest known risks of cardiovascular death (Gansevoort et al., 2013). Indeed, the increased risk of cardiovascular disease implies that the life-time expectancy is reduced by ~17 years for a 30-year old patient with chronic kidney disease Stage 5 (Gansevoort et al., 2013).

The risk factors for cardiovascular disease in patients with chronic kidney disease include classical factors: hypertension, dyslipidemia, (pre)diabetes, and insulin resistance, and also risk factors characteristic for chronic kidney disease; such as metabolic disturbances, uremic

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toxins, protein glycation, increased oxidative stress, and increased inflammation (Stenvinkel et al., 2008; Himmelfarb et al., 2002). Hence, both experimental and clinical studies point towards chronic kidney disease-specific pathogenic processes in the uremic vasculopathies (Drueke et al., 2010; Gansevoort et al., 2013; Stenvinkel et al., 2008), which include both atherosclerosis (Recio-Mayoral et al., 2011; Litwin et al., 2009, 2008; Yilmaz et al., 2011) and extensive calcifications of the medial layers of the large arteries (Goodman et al., 2000). This review will describe and discuss current knowledge about mechanisms accelerating atherosclerosis in uremia, with a particular focus on accumulating evidence on the putative roles of apoB and apoM.

2. Mechanisms that may accelerate uremic atherosclerosis

2.1. ApoB containing lipoproteins

Atherosclerosis is a slowly progressing disease of the arterial intima, where dyslipidemia, inflammation, and endothelial dysfunction are important pathogenic hallmarks. The dyslipidemia in uremic patients, as judged from qualitative changes of lipid concentrations in plasma, is relatively mild. Often, plasma triglycerides are increased reflecting increased plasma VLDL, whereas HDL can be decreased or unaltered in a setting of unaltered total plasma cholesterol (Keane et al., 2013; Reiss et al., 2015; Kwan et al., 2007). Initiation and progression of atherosclerosis is fuelled by high plasma concentrations of the apoB containing lipoproteins, *i.e.* VLDL and LDL. Thus, in the setting of increased plasma VLDL and/or LDL cholesterol, an increased fraction of the apoB-containing lipoproteins will enter the arterial wall, where they can either diffuse back to the circulation, or be bound to arterial wall proteoglycans (reviewed in Nordestgaard et al. (1994) and Camejo et al. (1998)). Once bound, the apoB-containing lipoproteins can be enzymatically modified by enzymes secreted from macrophages residing in the vessel wall or chemically modified by reactive oxygen species (Bae et al., 2009; Bhakdi et al., 1995). These processes increase the atherogenicity of the lipoprotein particles. As such, oxidation, carbamylation (a non-enzymatic post-translational modification mediated by cyanate (a decomposition product of urea) (Verbrugge et al., 2015)), or glycosylation of the apoB moiety increases the likelihood that the LDL is taken up by macrophages and accelerates the formation of foam cells, a pathognomonic hallmark of atherosclerosis.

Qualitative changes in the apoB moiety caused by a uremic milieu may be more important than quantitative, when it comes to the atherogenicity of VLDL and LDL in patients with chronic kidney disease (Keane et al., 2013). Hence, even though the plasma concentration of LDL is often not affected by chronic kidney disease (Reiss et al., 2015; Vaziri, 2014; Keane et al., 2013), the clearance of apoB in LDL is decreased in uremic patients (Kwan et al., 2007; Ikewaki et al., 2005). Hence, the median residence time of apoB in LDL was 4.6 days in hemodialysis patients *versus* 2.2 days in control subjects (Ikewaki et al., 2005). This allows for higher levels of modification of apoB/ LDL by oxidation, glycation, and/or carbamylation. Indeed, increased LDL oxidation (Samouilidou et al., 2012; Ribeiro et al., 2012; Bro et al., 2007, 2008), and apoB glycation (Bucala et al., 1994) have been reported in patients and/or animal models with chronic kidney disease. Moreover, carbamylation of plasma proteins is increased and associated with a higher mortality rate in patients with end stage renal disease (adjusted hazard ratio=2.3 and 2.4 for highest *versus* middle and highest *versus* lowest tertile of carbamylated proteins systemically, respectively) (Koeth et al., 2013). In mice, moderate uremia increases LDL carbamylation – and atherosclerosis (Apostolov et al., 2010). Of note, in the latter study, carbamylated LDL accumulated in the atherosclerotic lesions (Apostolov et al., 2010). In addition to accelerating foam cell formation, modification(s) of LDL also promote endothelial dysfunction (Stancu et al., 2012). Thus, with the implementation of sensitive methods such as mass spectrometry in clinical diagnostic laboratories, the road has been paved for studies on "modified" apoB as a risk predictor and therapeutic (pseudo) target for cardiovascular disease prevention in patients with chronic kidney disease.

Notably, patients with chronic kidney disease also have increased plasma levels of a peculiar apoB-containing lipoprotein subclass, *i.e.* lipoprotein(a) (Kimak et al., 2000; Bergesio et al., 2001; Aggarwal et al., 2010; Ribeiro et al., 2012; Kronenberg et al., 2000). As for LDL, the increased plasma concentration probably reflects increased residence time and, as such, increased risk of undergoing chemical modifications (Kronenberg et al., 2007). In patients with type 2 diabetes, elevated plasma concentrations of lipoprotein(a) are associated with decreased estimated GFR (Lin et al., 2015) and lipoprotein(a) can serve as a prognostic marker of development of chronic kidney disease (Yun et al., 2016). Of note, lipoprotein(a) accelerates atherosclerosis in uremic mice (Pedersen et al., 2010b) and increased intima media thickness has been detected in chronic kidney disease patients with increased lipoprotein(a) concentrations (Aggarwal et al., 2010). Finally, high lipoprotein(a) levels are associated with poor prognosis after percutaneous coronary intervention in patients with chronic kidney disease (Konishi et al., 2016). Combined, these data could suggest that lipoprotein(a) may be causally involved in acceleration of atherosclerosis in uremic settings. If so, lipoprotein(a) could serve as a therapeutic target to reduce cardiovascular risk in patients with chronic kidney disease.

Fig. 1 summarizes key characteristics of uremic atherosclerosis, including the increased retention and modification of apoB-containing lipoproteins.

2.2. The endothelial barrier

In addition to the plasma concentration and degree of lipoprotein/ apoB modification, the accumulation of VLDL and LDL in the arterial intima is crucially affected by the ability of the endothelial barrier to prevent influx of the plasma lipoproteins. Chronic kidney disease is associated with endothelial dysfunction, as measured by alterations in flow-mediated endothelium dependent vasodilatation in patients with chronic kidney disease compared to healthy controls (Bolton et al., 2001; Thambyrajah et al., 2000; Recio-Mayoral et al., 2011; Yilmaz et al., 2011) and by increased plasma concentration of soluble vascular cellular adhesion molecule (VCAM)-1 and soluble intercellular adhesion molecule (ICAM)-1 (Bro et al., 2004; Bonomini et al., 1998).

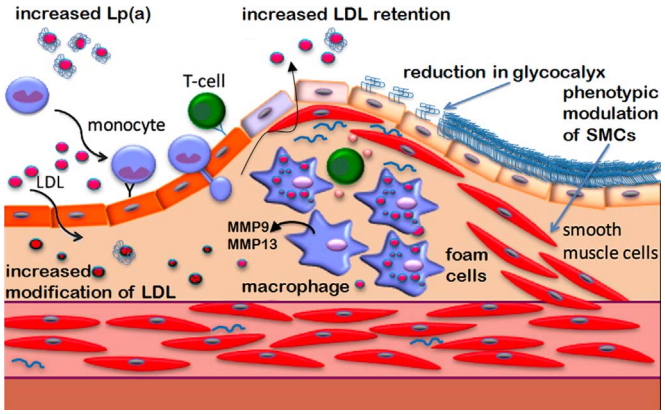

Fig. 1. Characteristics of uremic atherosclerosis. Uremia is associated with increased plasma concentration of the atherogenic Lp(a) particles, endothelial dysfunction, and thinning of the glycocalyx lining the arterial wall. This results in increased vascular permeability and increased influx of macromolecules such as LDL and Lp(a) into the arterial intima. Increased oxidation and carbamylation of LDL particles in the arterial wall increases the binding to proteoglycans and thus the retention time of LDL. Furthermore, the modifications promote the uptake of the lipoproteins into macrophages/foam cells. The uremic environment also leads to increased phenotypic modulation of vascular smooth muscle cells (SMCs). The figure is adapted from Aarup 2016.